MAY 19 1922

VOLUME 29 NUMBER 5

ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — LOUIS V. HAMMAN, Baltimore

GEORGE DOCK, St. Louis — WARFIELD T. LONGCOPE, New York

W. S. THAYER, Baltimore

MAY 15, 1922

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

FEBRUARY, 1922. NUMBER 2

Tracheal and Bronchial Stenosis as Causes for Emphysema. C. F. Hoover, M.D., Cleveland.

A Study of Microlymphoidocytic Leukemia, with the Report of a Case. Solomon Fineman, M.D., M.A., Minneapolis.

Intracutaneous Reactions in Lobar Pneumonia. George H. Bigelow, M.D., Boston.

Clinical Studies on the Respiration. VIII. The Relation of Dyspnea to the Maximum Minute-Volume of Pulmonary Ventilation. Cyrus C. Sturgis, M.D.; Francis W. Peabody, M.D.; Francis C. Hall, M.D., and Frank Fremont-Smith, Jr., M.D., Boston.

Position and Activities of the Diaphragm as Affected by Changes of Posture. Roy D. Adams, M.D., and Henry C. Pillsbury, M.D., Major, M. C., U. S. Army, Washington, D. C.

Auriculoventricular Rhythm and Digitalis. Henry R. Richardson, M.D., New York.

A Case of Disseminated Miliary Tuberculosis in a Still-Born Fetus. R. C. Whitman and L. W. Greene, Boulder, Colo.

A Convenient Electrode for Experimental Electrocardiographic Work. Carl S. Williamson, M.D., Rochester, Minn.

Book Review.

MARCH, 1922. NUMBER 3

Clinical Studies on the Respiration. IX. The Effect of Exercise on the Metabolism, Heart Rate and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease. Francis W. Peabody, M.D., and Cyrus C. Sturgis, M.D. With the Assistance of Bertha L. Barker and Margaret N. Read, Boston.

Studies in Diabetes Insipidus. Water Balance and Water Intoxication. Study I. James F. Weir, M.D.; E. Eric Larson, M.D., and Leonard G. Rowntree, M.D., Rochester, Minn.

A Hitherto Undescribed Tumor of the Base of the Aorta. George R. Herrmann, M.D., and Montrose T. Burrows, M.D., St. Louis.

Circulatory Compensation for Deficient Oxygen Carrying Capacity of the Blood in Severe Anemias. George Fahr and Ethel Ronzone, Madison, Wis.

Bacillus Acidophilus and Its Therapeutic Application. Leo F. Rettger, Ph.D., and Harry A. Cheplin, Ph.D., New Haven, Conn.

The Efflux of Blood from the Carotid Artery of the Dog and Its Expression by a General Empirical Formula. Halbert L. Dunn, B.A., M.A., Minneapolis.

Study of Blood Sugar Curves Following a Standardized Glucose Meal. W. H. Olmsted, M.D., and L. P. Gray, M.D., St. Louis.

Book Reviews.

APRIL, 1922. NUMBER 4

Observations on Paroxysms of Tachycardia. H. M. Marvin, M.D., and Paul D. White, M.D., Boston.

Renal Glycosuria. D. S. Lewis, M.D., Montreal, Canada.

Chemical Studies of the Blood and Urine of Syphilitic Patients Under Arsphenamin Treatment, with a Note on the Mechanism of Early Arsphenamin Reactions. Charles Weiss, Ph.D., and Anna Corson, B.Sc., Philadelphia.

Studies in the Variation of the Length of the Q-R-S-T Interval. G. E. Fenn, M.D., Chicago Heights, Ill.

Postoperative Pulmonary Complications. Elliott C. Cutler, M.D., and Alice M. Hunt, R.N., Boston.

The Pathology of Cirrhosis of the Liver. An Historic-Pathologic Study. Frederick Eppler, M.D., Spokane, Wash.

The Antidiuretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus. Herrmann L. Blumgart, M.D., Boston.

The Vital Capacity in a Group of College Students. A. W. Hewlett, M.D., and N. R. Jackson, M.D., San Francisco.

The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anemia. Joseph T. Wearn, M.D., Sylvia Warren and Olivia Ames, Boston.

Blood Pressure and Pulse Rate Levels. First Paper: The Levels Under Basal and Daytime Conditions. T. Addis, San Francisco.

Book Reviews.

COPYRIGHT, 1922, BY THE AMERICAN MEDICAL ASSOCIATION

Archives of Internal Medicine

VOL. 29 MAY, 1922 No. 5

STUDY OF SOME CASES OF DIABETES INSIPIDUS WITH SPECIAL REFERENCE TO THE DETECTION OF CHANGES IN THE BLOOD WHEN WATER IS TAKEN OR WITHHELD*

C. D. CHRISTIE, M.D., AND G. N. STEWART, M.D.
CLEVELAND

Several years ago[1] we published a study of a case of diabetes insipidus in which, among other points, attention was directed to the question, whether any well marked changes could be detected in the blood when the water intake was greatly restricted or water taken at discretion. The patient had an enormous diuresis and a correspondingly great thirst, so that the conditions seemed unusually favorable for the inquiry. The conductivity of the serum and the relative volume of the serum and corpuscles were selected for study because the conductivity can be measured with great accuracy, and from the conductivities of the serum and blood the percentage volume of serum can also be obtained to a close approximation. Even when great changes were taking place in the rate of absorption, elimination and transportation of water, it was found that the two quantities measured altered only very slightly, although there seemed to be a small increase in the conductivity and a small decrease in the relative volume of the serum when water was severely restricted. But the extreme variation for the conductivity of the serum was only 5 per cent. in observations made at an interval of five days (from 78.6 to 82.5 were the extreme values of $K \times 10^4$ at 5 C.). The percentage volume of serum varied from 83 to 79, again about 5 per cent. The woman had a severe anemia. In the absence of a greater number of observations than it proved possible to obtain on this patient, we cannot be quite sure that even the small differences observed were directly related to the changed intake or output of water.

We have since observed two additional cases. In neither case, however, was the diuresis as great as in the first case. Only in one of the cases (Case 1) were we able to obtain what we considered a fairly sufficient number of observations. They are summarized in Table 1.

*From the Department of Medicine of Lakeside Hospital and the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Christie, C. D., and Stewart, G. N.: Arch. Int. Med. **20**:10 (July) 1917.

TABLE 1.—Conductivity and Relative Volume of Blood Serum in C. S.

Date	K × 10⁴ at 5 C.		Percentage Volume of Serum		Remarks
	Serum	Blood	Electrical Method	Hematocrit	
Feb. 6, 9:30 a. m.	74.6 74.6	21.8 21.7	44.4 44.3	26.5 (10 m.), 40.5 (40 m.), 43 (60 m.)	After 25½ hours without food or water. Duplicate blood samples
10:00 a. m.	75.4	21.0	42.6	38 (30 m.), 39 (40 m.), 40 (55 m.), 41 (65 m.)	Food and 2,000 c.c. water taken from 9:30 to 10 a. m. Water taken thereafter as desired
3:30 p. m.	76.4 76.4	25.9 25.9	50.2 50.2	37 (15 m.), 47 (45 m.), 48 (61 m.)	Duplicate blood samples
Feb. 7, 9:30 a. m.	75.9	28.8	55.1	45.5 (15 m.), 51.5 (45 m.), 52.5 (55 m.)	Abstention from water and food begun at 9:30 a. m. Means of duplicate blood samples
Feb. 8, 10:45 a. m.	76.8	29.4	55.3	41 (10 m.), 51.5 (40 m.), 53.5 (60 m.)	After 25¼ hours without food or water. Means of duplicate blood samples
11:15 a. m.	75.7 75.7	28.1 28.1	54.1 54.1	41.5 (10 m.), 53 (40 m.), 54 (60 m.)	Food and 2,440 c.c. water taken from 10:45 to 11:15 a. m. Duplicate blood samples
5:00 p. m.	77.0	33.5	61.1	50 (10 m.), 57 (25 m.), 60 (50 m.)	Means of duplicate blood samples. Water at discretion since 10:45 a. m.
Feb. 9, 9:30 a. m.	76.8	31.6	58.6	50 (10 m.), 55 (25 m.), 58 (50 m.)	Abstention from water and food begun at 9:30 a. m.
Feb. 10, 11:00 a. m.	75.4	30.2	57.6	41 (10 m.), 52 (35 m.), 54 (50 m.)	After 25½ hours abstention
11:30 a. m.	75.6	28.2	54.4	41 (10 m.), 50 (35 m.), 52 (50 m.)	After taking food and 2,560 c.c. water from 11 to 11:30 a. m. Thereafter at discretion
5:45 p. m.	77.5	35.2	63.0	38 (10 m.), 54 (35 m.), 55.5 (50 m.)	
Mar. 10, 11:00 a. m.	73.5	31.3 32.1*	60.7	56 (10 m.), 58 (25 m.), 58.5 (35 m.)	Abstention from water and food begun
Mar. 11, 11:00 a. m.	80.7 81.0*	34.5 35.2*	59.6 60.3	52.5 (10 m.), 57 (25 m.), 58 (40 m.)	After 24 hours abstention
Apr. 20, 11:00 a. m.	75.4	30.0	57.3	.....	Abstention from water and food begun
Apr. 21, 11:00 a. m.	72.8 72.0*	29.3 28.5*	58.2 57.6*	49 (11 m.), 55 (31 m.)	After 24 hours abstention
Apr. 23	78.0 78.5*	32.3 33.1*	58.7 59.4*	45.5 (10 m.), 52 (20 m.), 53.5 (31 m.)	After 24 hours abstention from food and water

* Specimens obtained after injection of 12 c.c. congo red solution.

The observations were made at different times during eleven weeks, and the relative constancy of the serum conductivities, in spite of the changes imposed in the intake of water and the accidental changes which might be expected to occur over so long a period, is quite striking. The greatest variation was from 72.8 to 80.7, and the average of all the observations 76. The values obtained after injection of congo red solution for estimation of the blood volume are left out in calculating the average, although there would be practically no change if they were included, since the quantity injected causes no sensible alteration in the conductivity. The variation in the percentage of serum was greater than that in the serum conductivity, from 42.6 to 63 per cent., the average percentage for all the observations being 55.7. It so happens that all the serum percentages in the first series of observations (February 6) are lower than in any of the other series. It is not known that this was due to any experimental error. The only error which could possibly have caused such a result, so far as we can see, would be the loss of some of the serum in the manipulations before the blood was brought to the laboratory. But it is very difficult to understand how this could have affected all the specimens. Also duplicate specimens were taken in two observations, and the duplicate determinations are identical. It seems, therefore, more likely that the observations are correct, and that, for some reason unknown to us, there was a considerable increase in the relative volume of serum between February 6 and February 7. The hemoglobin content was seen to diminish somewhat throughout the series of experiments, accompanied by a slight diminution in the erythrocyte count. The average quantity of blood taken for each determination was not less than 20 c.c., so that it is possible that the mere loss of blood might, in part at least, account for this. The conductivities of the serum specimens of February 6 are not out of line with those of the rest of the series. If the serum percentages of February 6 are omitted the variation for the rest of the observations is from 54.1 to 63 per cent. and the average 58. There was only slight anemia in this patient, the erythrocyte count being in the neighborhood of 5,000,000, at the beginning, declining to 4,500,000 toward the end of the period.

As in the previously reported case, the percentage of serum was determined by the hematocrit as well as by the electrical method. It will be seen, as before, that the longer the centrifuge is turned the closer does the hematocrit reading approximate to the result of the electrical determination. The number of minutes rotation of the hematocrit (at about 4,000 turns a minute) is given in parentheses after the corresponding serum percentages.

The general plan of the observations was as follows: The patient being on his usual diet and taking water at discretion, a blood sample

(or generally two samples for duplicate determinations) was obtained, and the blood defibrinated. The electrical conductivity of the blood and serum and the percentage volume of serum were determined. The patient was then deprived of food and water, in the case of C. S. (Case 1) for twenty-four hours or longer, as he bore the deprivation well. Blood samples were obtained at the end of the period. Then he was allowed food and as much water as he could drink, and blood drawn at the end of thirty minutes, and again at the end of five or six hours, water and food being taken. Several sets of observations of this type were made on C. S. In none was there any material difference in the percentage of serum in the samples taken before and at the end of the period of abstention from water. The conductivity of the serum was also practically unchanged, except in the observations of March 10 to 11, when there was an apparent increase of about 10 per cent. at the end of twenty-four hours abstention from water.

The samples taken half an hour after renewed water ingestion showed practically no change in the serum conductivity, while in several of the sets of observations it seemed that a slight diminution in the percentage of serum occurred. More striking was the increase in the percentage of serum in the samples drawn from five to six hours after the taking of water had been resumed. This is seen in the observations of February 6, February 7 to 8, and February 9 to 10. The increase in the relative volume of the serum was not apparently accompanied by any diminution in the concentration of the salts, since the serum conductivity remained unaltered, or if anything, underwent a slight increase.

In Case 2 (U.A.), like Case 1, one of medium severity, the range of variation in the conductivity of the serum in all the observations was from 77.3 to 86.8. Although the mean of all the observations (82.2) was somewhat higher than in Case 1, the maximum range was about the same. However, the number of observations obtained in Case 2 was smaller than in Case 1, and they were spread over a much shorter period. In the most complete series in Case 2 (May 5 and 6) (Table 2) there was an increase in the conductivity of the serum after abstention from water for twelve hours (from 79.2 to 86.8. This was accompanied by a more marked diminution in the percentage volume of the serum (from 70.9 to 58.3 per cent.). On taking water, the proportion of serum increased. However, in the first experiment (April 20 to 22) when abstention was carried to the possible limit in this case (twenty-seven hours) a slight diminution of the conductivity was seen (from 82.0 to 77.3) accompanied by a marked increase in the proportion of the serum, while on April 30 the ingestion of 2 liters of water in twenty minutes after twelve hours abstention was associated with a slight increase in the conductivity of

TABLE 2.—Conductivity and Relative Volume of Blood Serum in U. A.

Date	K × 10⁴ at 5 C.		Percentage Volume of Serum		Remarks
	Serum	Blood	Electrical Method	Hematocrit	
Apr. 20	82.0	34.7	58.0	34 (14 m.), 45 (22 m.), 48 (29 m.), 50.5 (37 m.) 53 (49 m.)	Before abstention from water
Apr. 22	77.3	44.1	74.0	63 (14 m.), 66.5 (20 m.), 68 (30 m.), 68.5 (35 m.)	After 27 hours abstention
Apr. 26	79.0	33.4	59.5	52 (15 m.), 56 (23 m.), 58 (33 m.)	Water taken at discretion since April 22
Apr. 30, 10:00 a. m.	82.8	36.1	60.0	45 (10 m.), 52.5 (20 m.), 54.5 (30 m.)	After 12 hours abstention from water
10:20 a. m.	85.6	30.1	50.6	20 (10 m.), 39 (20 m.), 43.5 (30 m.), 46 (40 m.)	After 2,000 c.c. water had been taken in 20 minutes
May 5	79.2	42.8	70.9	60 (10 m.), 64.5 (20 m.), 66 (27 m.)	Before abstention from water
May 6, 10:30 a. m.	86.8	36.9	58.3	53 (10 m.), 55.5 (20 m.), 56 (25 m.)	After 12 hours abstention from water
11:00 a. m.	84.8	42.9	66.3	53 (10 m.), 60 (20 m.), 61.5 (25 m.), 63 (30 m.), 64.5 (37 m.)	After 1,575 c.c. water had been taken in 30 minutes

TABLE 3.—Conductivity and Relative Volume of Blood Serum in C. V.

Date	K × 10⁴ at 5 C.		Percentage Volume of Serum		Remarks
	Serum	Blood	Electrical Method	Hematocrit	
Nov. 29	80.2	29.5	53.1	43.5 (12 m.), 47 (18 m.), 49 (25 m.)	Before abstention from water and food
Nov. 30	....	....	....	42 (22 m.), 44 (32 m.), 45 (38 m.)	At end of 24 hours abstention from water
Nov. 30	87.1	30.9	49.4	....	After food and water had been taken at discretion for 1 hour

the serum, and a distinct diminution in the proportion of serum. We prefer not to attempt a hypothetic explanation of these variable results, simply pointing out that in Case 2 the relative volume of the serum was more variable than in Case 1, the extreme range being from 50.6 to 74 per cent. and the average of all the observations 62 per cent. It should be noted that in Case 2 deprivation of water was not nearly as well borne as in Case 1, the patient complaining much more of thirst. Also U.A. (Case 2) was allowed food during the period of deprivation of water, although he ate less than usual.

The observations in these cases illustrate, perhaps, even more clearly than those previously published, how trifling the changes in the concentration of the blood plasma, as regards the electrolytes, may be when great changes in the ingestion, excretion and transportation of water are in progress. So far as our experience goes it would seem that it is only in exceptionally favorable circumstances that even minute changes in the conductivity of the serum, a quantity capable of being measured to so considerable a degree of accuracy, can be detected with certainty. Observations which profess to demonstrate considerable and constant variations, associated with the taking or withholding of water should, we think, be received with reserve.

The relative volume of the blood plasma may undergo somewhat greater variations. This agrees with the conclusion of Farkas,[2] in an extensive research on the influence of water and salt given with the food on the water content of the organs in some of the domestic animals. In sheep caused to drink large quantities of water with or without sodium chlorid, the osmotic pressure and the concentration of the electrolytes remained the same; but the water content of the blood was increased in the sheep which received salt as well as water. According to Adolph,[3] the drinking of isotonic salt solution by normal persons is accompanied by a measurable diminution in the hemoglobin content of the blood, indicating some increase in the water content. The possibility should not be lost sight of that in cases of diabetes insipidus the variations may be even less than in normal individuals, the urine secreting mechanism being, perhaps, even more responsive to slight changes in the blood, or the tissues less capable of storing any excess of water.

We do not intend to discuss the mechanism by which the osmotic pressure and the concentration of electrolytes in the plasma (as measured by the electrical conductivity) are maintained relatively constant during the absorption or excretion of large quantities of water. The exchange between the erythrocytes and the plasma, as well as the exchange between the tissue liquids and the plasma through the

2. Farkas, K.: Mitth. aus. d. Königl. Ungar. Tierphysiol. Versuchsstation in Budapest. No. 3, Berlin, 1908; Landwirtschaftliche Jahrb., 1908.
3. Adolph, E. F.: J. Physiol. **55**:114, 1921.

capillary walls, must play a part. As to the relative volume of plasma and corpuscles, although the changes were probably greater than those in the conductivity of the serum, they were too small in amount, and not constant enough in sign, to permit the assumption that when water was withheld, any important part of the water which continued to be excreted could have been credited to a diminished water content of the blood, or that when water was again taken, any important part of it went to recoup the blood for its previous loss. The chief changes must have been in the tissue water. The slight apparent diminution in the percentage of serum in the first half hour after resumption of water intake, if it is a genuine diminution, might possibly have been associated with a preliminary speeding up of the diuresis. The increase in the proportion of serum a few hours later, perhaps to something more than the amount present at the beginning of the period of abstention, is most naturally associated with a rapid absorption slightly outstripping the diuresis. However, this is not the only possible explanation, and as has been previously said, speculations founded on such data as we have been able to obtain would, in the present state of our knowledge, be of little value. This is well illustrated by the marked increase in the proportion of serum, accompanied by a slight decrease in the conductivity, seen in the observations of April 20 to 22 in Case 2, after twenty-seven hours abstention from water. Whether the fact that some solid food was taken in this case influenced the result, it is impossible to say.

REPORT OF CASES

CASE 1.—C. S., male, married, aged 39, was admitted to the Lakeside Hospital medical service, Feb. 3, 1921.

Past History.—Essentially negative, aside from an attack of pneumonia five years ago. No history of any venereal infection.

Present Illness.—The patient dates his present trouble from July, 1920, when he noticed that he was becoming more irritable and much more easily fatigued. He had been an active man, but he now became so tired that his one desire was to lie down and sleep. He arose late each morning and retired early, and usually spent most of his Sundays in bed. Four months ago he began to have headaches, which he described as "heavy aches," coming every two or three days and lasting from a few minutes to half a day. They seemed to distress him more at night, and would sometimes awaken him. About one month after the headaches started, he noticed that he was gradually drinking more water each day and was passing an excessive quantity of urine. He said that his thirst reached such a degree that he would drink from three to four glasses of water every half hour and pass a corresponding amount of urine.

Physical Examination.—The patient is a well developed and well nourished man, and gives the appearance of being in good health. He is extremely neurotic, apprehensive, prone to complain and very restless. There is considerable dryness of the skin and a slight anemia. The eyes and eye grounds are normal. There is no evidence of cardiac enlargement. Blood pressure is not elevated. There is no acceleration of the pulse rate; no abnormal physical signs about the abdomen or the extremities. A complete neurologic examination revealed no abnormal findings.

Urine.—The urine was pale and of low specific gravity; no albumin or sugar. The quantity varied from 6 to 10 liters in the twenty-four hours.

Blood.—The blood showed: hemoglobin from 80 to 90 per cent. (Tallquist); white blood count, from 5,000 to 7,000; red blood count varied from 4,500,000 to 5,000,000. Blood sugar estimations showed from 0.085 to 0.090 gm. per hundred c.c. (by Lewis and Benedict method); blood urea varied between 0.025 and 0.032 gm. per hundred c.c.

Spinal Fluid.—Lumbar puncture revealed no increase in pressure; fluid normal in color; no cells. The Wassermann, globulin and gold chlorid tests were negative.

Head.—Roentgenograms of the region about the sella turcica showed no evidence of a pathologic process.

Kidneys.—Renal test meals, given when the patient was getting three daily intramuscular injections of 1 c.c. of a pituitary extract (pituitrin) showed an output of from 2 to 3 liters and that the patient's kidneys were quite able to concentrate the urine.

Dec. 15, 1921, the patient, who had become insane, shot himself in the left chest and died December 25. Diagnosis: "encysted hematoma, empyema and collapse of the left lung." The necropsy gave no information as to the possible cause of the polyuria. The pathologic examination of the brain, including the pituitary, showed nothing abnormal.

CASE 2.—U. A., male, single, aged 16; admitted to Lakeside Hospital medical service, April 7, 1920.

Past History.—He had had when a child the ordinary diseases.

Present Illness.—He dates his present trouble from the time he was 5 years old, when he had a cold and was feverish one night, and began drinking water excessively and urinating frequently. He was apparently worse at that time, from the statement of his parents, as he was not allowed to enter school until he was 7 years of age because of the trouble. Since the complaint began, eleven years ago, there has been no marked abatement of symptoms.

Physical Examination.—The patient is well developed and well nourished, and does not have the appearance of being ill. There are a few small brown pigmented areas over the face. The eyes are normal; the pupils react to light and accommodation; eye grounds are normal; no disturbance in the field of vision. The heart is not increased in size, and the pulse is regular and of good volume. The systolic blood pressure varied between 130 and 120 and the diastolic between 79 and 60. Examination of the abdomen and extremities was negative. A complete neurologic examination revealed nothing pathologic.

Urine.—The urine varied between 5 and 10 liters per twenty-four hours. It was pale, and the specific gravity varied between 1.002 and 1.005, except when the fluid intake was restricted or when the patient was given pituitary extract (1 c.c. three times daily, intramuscularly), and then the output was cut down and the specific gravity elevated. No albumin, casts or sugar.

Blood.—The blood showed: hemoglobin, 90 per cent. (Tallquist); white cells, 10,000; red cells, 5,200,000. Blood sugar, 0.10 gm. per hundred c.c., and blood urea, 0.030 gm. per hundred c.c.

Head.—Roentgenograms of the region about the sella turcica revealed nothing abnormal.

Kidneys.—The phenolsulphonephthalein excretion was 78 per cent. in two hours.

Discussion of the Clinical Aspects of Cases 1 and 2.—There was nothing unusual about these cases other than that the patients had a diabetes insipidus of medium severity. Nothing was made out, either on physical examination or from the laboratory procedures, which gave us any clew to a possible etiology.

Both Cases 1 and 2 responded to the intramuscular injection of pituitary extract when given in 1 c.c. doses. The thirst and diuresis promptly subsided, and if three daily injections of 1 c.c. were given, the urine output could be cut down from 5 to 12 liters to below 2½ liters in the twenty-four hours. Feeding of the fresh pituitary gland to the patients had no effect, and the oral administration of commercial pituitary extract did not modify the diuresis. There was no evidence obtained from any of the tests for kidney function to bear out the contention of Erich Meyer [4] and others that the diuresis in diabetes insipidus is in any way associated with, or dependent on, a pathologic alteration in the kidneys. Both our patients had perfectly normal phenolsulphonephthalein excretions. There was no evidence of nitrogen retention in the blood; and when the diuresis was lessened by pituitary extract and the patients were put on a renal test meal their kidneys showed ample ability to concentrate the urine. These clinical observations bear out in the main the findings which we have reported in another case.[1]

In these two cases the condition was chronic, of long standing and of unknown etiology. A third case (C.V.) was studied in which the polyuria, apparently associated with a lesion of the base of the brain, came on suddenly, and disappeared after lumbar puncture.

CASE 3.—C. V., male, married, aged 28, was admitted to the Lakeside Hospital medical service, Nov. 27, 1920.

Past History.—This patient had had the ordinary diseases of childhood, and typhoid fever when about 11 years of age (?). At 25 years he had pneumonia, and for some time after was weak. He was thought to have tuberculosis of the lungs at that time and was advised to go to California, which he did. He came back apparently in good health, and then had influenza in February, 1920.

Present Illness.—April 29, 1920, after moving his household effects, at which he had worked very hard, riding around most of the day in a truck, he felt numb over the whole left side of his body. He said that he felt as if the left side of his body belonged to someone else. He was totally unable to move his left arm and hand and also his left leg. This paralysis disappeared in about two hours. It had never appeared prior to that time.

Since the attack of influenza and paralysis the patient enjoyed good health until last night (November 26) at 4 a. m., when he awakened with a dull headache, which he had not had for two years at least, and a slight vertigo, both of which persisted until today (November 27). As he awoke last night he says he had a most extreme sense of thirst in the interior of his nose and not in his mouth. He has since emphasized the fact that the thirst was in his nose and very intense. He also noticed that he had a markedly overfull bladder, which caused him pain above the pubic crest. When he voided urine he said he was sure that he passed more than a quart. His thirst persisted all day yesterday and is still present today in the same intensity. Yesterday he voided from 12 to 14 quarts of urine, and he says that he is maintaining the same average of urine output today. Today he feels weak and tired, in addition to his other complaints, and has a general soreness over his abdomen, which he attributes to his frequently overdistended bladder.

4. Meyer, Erich: Deutsch. Arch. f. klin. Med. **83**:1, 1905; Ztschr. f. klin. Med. **74**:352, 1912.

Physical Examination.—The patient is an intelligent young man, well proportioned and of healthy appearance. There were no abnormalities about the head, eyes, ears, nose and throat, except those detailed under the neurologic examination. There were a few enlarged lymph glands and a moderate uniform hypertrophy of the thyroid gland. Aside from a slight impairment in the movement of the left upper chest, the examination of the lungs was negative. The heart showed no evidence of enlargement or valvular defect. The pulse was not accelerated; systolic blood pressure was 125, diastolic, 80. The abdomen was normal and an examination of the rectum, genitalia and extremities revealed nothing abnormal.

Neurologic Examination.—The mentality of the patient is good and he cooperates well. Cranial Nerves: There was a loss of the sense of smell in the left side of the nose. The gross vision not impaired. There was a concentric limitation of the left visual field. The left pupil reacts more slowly to accommodation than the right. The external muscles of the eye were normal. There was impairment in the sense of touch and pain over the left forehead and zygomatic area. The lower and lateral part of face were unaffected. There was slight paresis of the left facial nerve. There was a diminution in both bone and air conduction in the left ear. There was impairment in the sense of taste and common sensation on the posterior third of the tongue, but muscles of palate and pharynx seemed intact. There was some atrophy of the left side of the tongue.

Sensory Examination.—There was a very gross impairment in all sensations over much of the left side of the body. This included primarily touch, but there was a corresponding diminution to pain, heat and cold and to vibration. The areas which were most markedly involved were the left forehead, left zygomatic area, left neck, left finger tips, distal phalanx of all toes on the left foot and the medial surface of left leg, etc. There was no ataxia; gait and station normal, and no impairment in complemental opposition; muscles were normal. Both skin and deep reflexes were apparently normal. There was nothing made out to suggest any involvement of the sympathetic nervous system.

Our conclusion from the neurologic examination was that the patient had a basilar lesion which was either a tumor or a serous meningitis.

Urine.—The urine was pale, with a specific gravity of 1.005. The urine never contained any pathologic elements.

Blood.—Blood examination showed hemoglobin, 100 per cent. (Tallquist); white blood cells, 7,000; red blood cells, 5,800,000.

Spinal Fluid.—About 8 c.c. of clear colorless fluid was removed by lumbar puncture. It contained 2 cells to the field; no increase in pressure or in the globulin content. The Wassermann was negative. Blood Wassermann was also negative.

Head.—Roentgenograms of the area about the base of and of the whole skull were negative.

Kidneys.—Phenolsulphonephthalein excretion was 57 per cent. in two hours, and a renal test meal, given after the diuresis had subsided, showed that the kidneys had ample ability to concentrate the urine.

Discharge Note.—This patient had polyuria for less than three days. It made its appearance early in the morning of November 27, and November 29 a lumbar puncture was done for diagnostic purposes, after which the polyuria disappeared, even though nothing pathologic was found in the spinal fluid and there was no increase in pressure. The patient, while the polyuria existed, excreted about 12 liters of urine per day. He had a severe headache for several days following the lumbar puncture. He was discharged from the hospital Dec. 7, 1920. His urine output had not exceeded 1,300 c.c. in any twenty-four hours after the lumbar puncture. There were no demonstrable changes in the neurologic signs on discharge.

Case 3 was one of severe polyuria of very acute onset. There was evidence that the patient had an intracranial lesion which was probably located at the base of the brain. It had apparently involved the olfactory nerve, the optic nerve peripheral to the chiasma and the fifth, seventh, ninth and twelfth cranial nerves, the involvement probably being nuclear, with, perhaps, also some encroachment on the sensory areas in the thalamic region. Our impression was that there was either a tumor or a serous meningitis at the base. A lumbar puncture was decided on for aid in diagnosis. Although the cerebrospinal fluid was not under increased pressure and its examination was negative, after this procedure the increased thirst and diuresis disappeared. In Case 1 lumbar puncture was also done, but there was no effect on the thirst or diuresis.

There has been no return of the diuresis since C. V. (Case 3) left the hospital, and for some months he appeared to be in good health. However, after from three to four months, he began to show signs of loss of mental balance, the derangement taking largely a religious turn, and he had to be discharged from his work. He is now (October, 1921) in a sanitarium, suffering from "nervous breakdown."

Any hypothesis which we could advance as to the cause of the polyuria in this case would be mere conjecture. The course of the onset, the recovery following the lumbar puncture and the fact that there has probably been no increase in the neurologic signs since he left the hospital, make the diagnosis of serous meningitis seem the most likely. Herrick [5] reported a case in 1912 in which the polyuria ceased after lumbar puncture, and in 1918 Cammidge [6] reported a case. Cammidge thought his patient had a serous meningitis due to a parasyphilitic state.[7]

It had been intended to study the blood in the same way as in the other cases. But owing to the disappearance of the polyuria after lumbar puncture only two sufficient samples of blood were obtained, one before abstention from water was begun and the other one hour after the taking of water had been resumed. The first specimen was secured on the day when lumbar puncture was done and the second on the following day when the diuresis had already subsided. The conductivity of the serum (Table 3) in the second sample was somewhat greater than in the first and the percentage of serum was somewhat less. The blood specimen obtained at the end of the twenty-four hour period of abstention was so small that only a hematocrit determination could be made. The percentage of serum after thirty-eight minutes rotation was 45, whereas in the sample taken before

5. Herrick: Arch. Int. Med. **10**:1 (July) 1912.
6. Cammidge, P. J.: Practitioner **105**:244, 1918.
7. We desire to express our thanks to Dr. R. G. Pearce, Akron, Ohio, for referring Case 3 to us for study.

abstention it was 49 after twenty-five minutes rotation. Probably, therefore, there was some diminution in the serum percentage at the end of the period of abstention. At any rate there was no increase. It is impossible from the hematocrit determination alone to say more than this.

SUMMARY

The regulation of the excretion of water by the kidneys was studied in two cases of diabetes insipidus presenting the typical features, and in one case of polyuria of acute onset, apparently associated with a brain lesion. In the last case the polyuria disappeared permanently after lumbar puncture, but the patient eventually developed symptoms of mental derangement.

Blood specimens obtained immediately before and immediately after a long period of complete deprivation of water (twenty-four hours or more) showed no definite differences in the electrical conductivity of the serum, which could be associated with changes in the rate at which water was being absorbed, transported and excreted, although the conductivity can be measured with great accuracy. The same was true of the percentage volume of serum.

Comparison of blood specimens procured within half an hour, and again after five or six hours, after the resumption of water drinking with the specimens obtained just before or just at the end of the period of water deprivation also revealed differences in the conductivity of the serum so slight and so inconstant that it was impossible to connect them definitely with changes in the intake of water.

The percentage of serum, in the observations which we were able to carry out completely, seemed to be somewhat greater in the specimens taken after five or six hours, than in the specimens taken half an hour after resumption of water drinking.

The regulation of the concentration of electrolytes in the plasma and of the relative volume of plasma and corpuscles in the blood was, therefore, at any rate as fine in these cases of diabetes insipidus, in spite of the great variations induced in the quantity of water transported, as in normal persons. It is possible, indeed, that in this condition the renal excretory mechanism is even less tolerant than normal of any excess of water in the blood, or the tissues less capable than normal of storing an excess of water.

As in the case previously published,[1] no evidence was obtained that the condition was associated with any pathologic change in the kidneys. The various tests of efficiency of renal function gave normal results. When pituitary extract was administered the kidney showed normal power of concentrating the urine.

CLINICAL CALORIMETRY. XXX. METABOLISM IN ERYSIPELAS*

WARREN COLEMAN, M.D., DAVID P. BARR, M.D
AND EUGENE F. DU BOIS, M.D.
WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM
NEW YORK

In the study of fever in the human subject it is difficult to select a disease which lends itself well to experimental conditions. Patients with certain fevers, such as pneumonia, are so seriously ill that one hesitates to make even the simplest observations. Some of the other fevers are so mild that they do not give one a chance to study high temperatures. In others, the possibility of contagion must be considered and it is hardly justifiable, for instance, to study measles or scarlet fever in a room adjoining a general ward. Typhoid fever, which is in many respects ideal for experimental work in the respiration calorimeter, was thoroughly investigated by Shaffer and Coleman [1] and later by the staff of the Russell Sage Institute of Pathology.[2]

It seemed desirable to determine whether other acute infectious diseases present phenomena similar to those of enteric fever. For this purpose erysipelas was chosen. There were several reasons for its selection. In the first place, the inflammatory process can be observed and a fairly good prognosis can be made from day to day. The temperature is high and the toxemia often severe and yet the patient is not exhausted by simple movement such as the necessary transfer from the bed to the calorimeter. Moreover, temperature fluctuations are often rapid. It was hoped that further information might be obtained concerning temperature regulation in the body.

In many respects, erysipelas was a disappointment from an experimental standpoint. Some of the patients were of alcoholic habits which dulled their intelligence and accentuated the usual delirium of the disease. Cooperation in the collection of twenty-four hour specimens was obtained with difficulty. The mental state of the patient often rendered calorimetric observations impossible at times when it would have been otherwise desirable to make them. The appetite was

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Shaffer and Coleman: Protein Metabolism in Typhoid Fever, Arch. Int. Med. 4:538 (Oct.) 1909.

2. Coleman, W., and Gephart, F. C.: Clinical Calorimetry. Paper 6, Notes on the Absorption of Fat and Protein in Typhoid Fever, Arch. Int Med. **15**:882 (May) 1915; Coleman, W., and Du Bois, E. F.: Paper 7, Calorimetric Observations on the Metabolism of Typhoid Patients with and Without Food, Arch. Int. Med. **15**:887 (May) 1915.

always capricious and it was many times impossible to induce the patients to take the requisite amount of food. Furthermore, the expected wide fluctuations of temperature were not observed in the calorimeter. Special efforts were made to observe these changes. Experiments were undertaken at night in the hope of obtaining the usual sharp drop in temperature during the morning hours. For some reason, however, fluctuations in temperature always seemed to be less marked when the patients were in the calorimeter than when they were in the erysipelas ward. The same difficulty was experienced in the study of falling temperature in tuberculosis.

Several determinations of the total heat production have been made in facial erysipelas by Riethus [3] and Grafe.[4] Riethus found an increase of 41 per cent. in the metabolism, Grafe, in one case with a temperature of 39.5 F, found the heat production 40 per cent. above the level which it assumed after recovery. Loening,[5] in a comparative study of the nitrogen losses in various fevers, published the results in eight cases of erysipelas. Rolland [6] in one case with a range of temperature between 37.5 and 39 C. gave 46 calories per kilo in the food with 12.1 gm. protein daily and found a negative nitrogen balance averaging 0.67 gm. per day. She considered this as evidence against a toxic destruction of body protein. Kocher [7] was able to administer to four erysipelas patients diets containing from 3,200 to 4,300 calories with only 1.8 to 2.2 gm. nitrogen. On such diets, normal men excrete only from 2 to 4 gm. nitrogen even though they perform severe muscular exercise. The nitrogen excretion of the erysipelas patients was from 9 to 20 gm. even after several days of this diet. Grafe,[8] one of the chief opponents of the theory of toxic destruction, confirmed these results. He gave an erysipelas patient a diet containing 66 calories per kilo and no protein. The urinary nitrogen dropped from 25.9 gm. to 7.7 gm. on the fifth day of the diet but would not fall below this point.

The various urinary constituents have been determined by most of the investigators who have studied the nitrogen metabolism. Unusually complete analyses were made by Kocher.[7] He found during the febrile

3. Riethus, O.: Beobachtungen über den Gaswechsel kranker Menschen und den Einfluss antipyretischer Medicamente auf denselben, Arch. f. exper. Path. u. Pharmak. **44**:239, 1900.

4. Grafe, E.: Untersuchungen über den Stoff- und Kraftwechsel in Fieber Zur Genese des Eiweisszerfalls bei Fieber und bei Arbeitsleistung, Deutsch. Arch. f. klin. Med. **101**:209, 1911.

5. Loening, K.: Experimentelle und klinische Untersuchungen über Eiweiss und Stoffwechsel im Fieber, Klin. Jahrb. **18**:199, 1908.

6. Rolland, A.: Zur Frage des toxogenen Eiweisszerfalls im Fieber des Menschen, Deutsch. Arch. f. klin. Med. **107**:440, 1912.

7. Kocher, R.: Ueber die Grösse des Eiweisszerfalls bei Fieber und bei Arbeitsleitung, Deutsch. Arch. f. klin. Med. **115**:82, 1914.

8. Grafe, E.: Zur Genese des Eiweisszerfalls im Fieber, Deutsch Arch. f. klin. Med. **116**:328, 1914.

periods a considerable increase in the excretion of creatinin. At the height of the disease, this reached from 2.4 to 2.6 gm. per day, the uric acid from 0.8 to 2.0 gm. and the ammonia from 1.8 to 3.0 gm.

Our own work includes eight observations on the basal metabolism of five patients during the acute stage of the disease. Two of the five were studied on the first day of normal temperature. The respiration calorimeter of the Russell Sage Institute of Pathology was employed. The methods have been described in Paper 4 [9] of this series. Observations were also made on the nitrogen equilibrium and on the weight curves during the infection.

The character of the cases studied can be judged from the following histories.

REPORT OF CASES

CASE 1.—Erysipelas of neck and back.

History.—Arshel A., a peddler, born in Russia, 29 years of age, was admitted Oct. 9, 1916, and discharged cured Oct. 24, 1916. He drinks one glass of beer a day and smokes cigarets to excess.

September 25 a boil developed on the left side of the back of the neck. It was incised on the twenty-eighth but the area of incision became red and swollen. The inflammation spread very rapidly until it covered the neck and back. He felt feverish but had no chill.

Physical Examination.—The patient is an undersized, fairly well developed and nourished young Jew, acutely ill but mentally alert and rather apprehensive. The tongue is moderately dry with a thick white coat. Lymph nodes are not enlarged. On the back of the neck is a small incision nearly healed. The area of inflammation extends from the hair line to two inches below the inferior angles of the scapulae and from the right to the left deltoid. The area is brawny and dark red in color and is sharply demarcated from the surrounding skin, but without a definitely raised edge. There are many broken blebs. The spleen is not palpable.

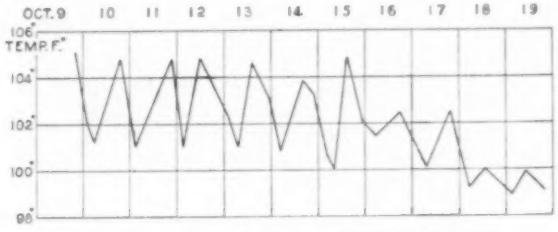

Fig. 1.—Arshel A. (Case 1) Temperature chart.

Laboratory Examination.—The urine shows a trace of albumin; no casts. Blood: October 16: Leukocytes, 25,000; polymorphonuclears, 93 per cent.

October 13 he was in the calorimeter from 10:30 a. m. to 2:30 p. m. October 14 the inflammation had extended to the elbow on the left side to within two inches of the elbow on the right. The inflammation of the back was

9. Gephart, F. C., and Du Bois, E. F.: Clinical Calorimetry, Paper 4, The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. **15**:835 (May) 1915.

less marked, and his general condition was improved. From 6 p. m. October 15 to 2:45 a. m. October 16 he was again in the calorimeter. By the twenty-first all active inflammation had disappeared and he was discharged as cured October 24.

Case 2.—Facial erysipelas.

History.—James W., a fireman born in the United States, 51 years of age, was admitted Oct. 11, 1916, and discharged as cured on Oct. 21, 1916. He had gonorrhea in 1896 without complications. He denies syphilis and says he does not drink.

October 9 he had noticed that the left side of his nose was swollen and red. He had a chill in the afternoon. During the next twenty-four hours the swelling spread rapidly over the left side of the face.

Physical Examination.—Patient is a well developed, poorly nourished, rather surly American, acutely ill. His tongue is red at the edges, shows a white coat and is very dry. Over the bridge of the nose and spreading over the entire left side of the face is a diffuse, red, hot area of inflammation. The edge is raised, firmly and sharply demarcates the area from the surrounding skin. The pulse is slow, full and dicrotic. The spleen is not palpable. Lymph nodes are not enlarged.

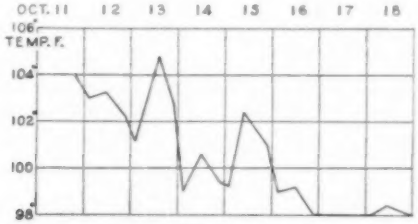

Fig. 2.—James W. (Case 2) Temperature chart.

Laboratory Examination.—Urine is negative. Blood Pressure: Systolic, 130 mm.; diastolic, 70 mm.

October 13 the area of inflammation had spread to include the left ear. The left eyelid was swollen and shut. On the fifteenth the right forehead and ear were swollen, tender and red. The condition of the left side of the face was much improved. October 17 he was placed in the calorimeter from 10:15 a. m. to 1:15 p. m. At that time his temperature was normal and most of the signs of inflammation had disappeared. Both ears were slightly swollen. The left ear was desquamating. He was discharged as cured October 21.

Case 3.—Facial erysipelas.

History.—Odysseus B., a cigaret maker, born in Greece, 46 years of age, was admitted Oct. 24, 1916, and discharged cured Nov. 1, 1916. He was operated on for fistula in ano in March, 1916, at an Italian hospital. He drinks two glasses of beer a day; no whisky.

October 20 he had a slight pain in the abdomen. On the afternoon of October 21 he had a severe chill with high fever. On the morning of October 22 he noted a slight redness on the right side of the nose. This spread gradually to the left side and ultimately covered his cheek and forehead.

Physical Examination October 27, 1916.—Patient is a well developed, fairly well nourished man, acutely ill. The tongue is moist with a thick, white coat. Over the left cheek, ear, forehead and scalp and over the right forehead, is a diffuse swelling, hot and tender, dark red in color, showing over a portion

of its periphery, particularly in the scalp, a distinct raised edge. The nose shows no abrasion. However, there is an occasional slight nasal hemorrhage. The throat is red but not swollen. The lymph glands of the neck are not enlarged. Over both lungs are a few scattered râles. Coughing is frequent. The spleen is not palpable.

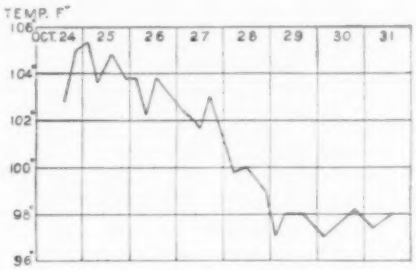

Fig. 3.—Odysseus B. (Case 3) Temperature chart.

Laboratory Examination.—Urine shows a faint trace of albumin; no casts. Blood: Leukocytes, 22,000; polymorphonuclears, 84 per cent.

October 27 he was in the calorimeter from 10:30 a. m. to 1:30 p. m. By the twenty-eighth the area of inflammation had increased in extent to cover the scalp to the occipital prominence and the neck for two inches posterior and inferior to the left ear. The inflammation, however, had decreased in intensity, desquamation had begun and recovery from that time was rapid. He was discharged, cured, October 31.

CASE 4.—Facial erysipelas.

History.—Robert H., a waiter, born in Germany, 38 years of age, was admitted Oct. 31, 1916, discharged as cured Nov. 10, 1916. He has been in this country since 1902. He drinks moderately of beer; no whisky. He has had gonorrhea several times; had a chancre in 1915, no secondaries.

October 27 he had some fever and muscular pains but no chill. He remained in bed until October 30, when he went to a choral club rehearsal. It was first noted there that his face was red and swollen. The swelling began on the nose and spread rapidly to both cheeks.

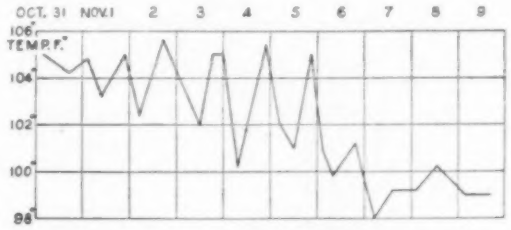

Fig. 4.—Robert H. (Case 4) Temperature chart.

Physical Examination.—Patient is a well developed and well nourished man, very nervous, acutely ill. The tongue is slightly dry and covered with a brown coat. Over the nose, the lower half of the forehead and the cheeks down to the angles of the mouth there is an edematous, red, hot, slightly tender area of inflammation, the edges of which are moderately raised and indurated and sharply demarcated from the surrounding skin. The eyelids are swollen and shut. The conjunctivae are red and edematous. At the angle of

the left jaw there is a moderately tender, nonfluctuating lymph node. The throat is slightly red. The lungs shows no signs although the patient coughs frequently. The spleen is easily palpable two finger breadths below the costal margin.

Laboratory Examination.—Urine shows a trace of albumin; no casts. Blood: Wassermann is negative.

November 3 the inflammation had spread to involve the whole face. From 11:22 a. m. to 4:22 p. m. he was in the calorimeter. November 4 the ears were involved but the severity of the inflammation of the face was less marked. Desquamation had begun. During the night, from 11:30 p. m. November 4 to 2 a. m. November 5, he was in the calorimeter. On the sixth a large grayish patch appeared on the uvula. A culture was negative for diphtheria. By the eighth the redness and swelling had disappeared from the face. A new area of inflammation had appeared on the back of the neck similar in character to the first one. Lymph nodes were no longer palpable. He was in the calorimeter from 11:30 a. m. to 2:30 p. m. By the tenth practically all signs of inflammation of the skin and the grayish patch on the uvula had disappeared. The spleen was still palpable below the costal margin. The heart murmur was still present. He was discharged as cured on November 13.

CASE 5.—Facial erysipelas.

History.—Joseph S., a sailor born in Russia, 25 years of age, was admitted Feb. 27, 1917, and discharged cured March 23, 1917. He had smallpox in Russia in 1902. He drinks moderately. He denies venereal infection.

During a boxing match February 25 he received a severe blow over his left eye and left ear. Two days later he was admitted to Bellevue Hospital with a hematoma and a marked cellulitis of the left eyelid and ear. By March 3 the wound of the eyelid had become definitely erysipelatous.

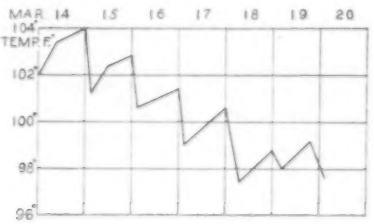

Fig. 5.—Joseph S (Case 5) Temperature chart.

Physical Examination March 6 (after development of erysipelas).—Patient is a muscular, well nourished, very surly young Russian, prostrated by disease; very toxic. The conjunctivae of both eyes are swollen, bright red and are exuding pus. There is a slight cloudiness of the right cornea. In the left upper eyelid there is a badly infected cut, extending the width of the lid and exuding pus. The erysipelatous area extends over the nose, both cheeks to the angle of the mouth on the right, to the neck on the left. The skin is red and indurated and there are numerous blebs containing purulent serum. In the upper part of the pinna of the left ear is a hematoma the size of a walnut. There is a wide sinus extending deep into the mass and exuding pus. There is no sign of rupture of the drum membrane, no evidence of infection of middle ear. The cervical nodes are enlarged and on each side is a diffuse, tender swelling about the region of the parotids. The tongue is dry and coated with brownish pus. Fauces are red and slightly swollen. The heart shows marked overaction. Lungs show a few scattered râles. The soft edge of the spleen is palpable one finger breath below the costal margin.

Laboratory Examination.—The urine is negative. Blood (March 6, 1917): Leukocytes, 7,000; polymorphonuclears, 75 per cent. Roentgen ray showed no fracture of skull.

March 6 he was in the calorimeter from 12 noon to 1 p. m. March 12 the cut on the eyelid was practically healed. The inflammation of the conjunctivae and the diffuse redness and swelling of the skin had almost disappeared. There was, however, a localized swelling over the upper right cheek and the bridge of the nose. When this was opened it discharged considerable amounts of pus. Following this he recovered rapidly and was dicharged as cured March 23.

The data of the calorimeter experiments are presented in Table 1. A summary of results will be found in Table 2.

DISCUSSION OF RESULTS

Basal Metabolism.—In the ten experiments the agreement between the total calories measured by direct and indirect calorimetry is deceptive. The calories by the direct method totaled 2,152.9 by the indirect method 2,118.6, a divergence of only 1.1 per cent. In the individual experiments, however, the divergence ranged between + 9.6 and — 13.5 per cent. Perhaps this discrepancy may be explained, in part, by the necessarily short periods during which some of the patients were observed. In typhoid fever,[1] it was found that during the first hour, some heat was probably lost in warming the bed frame and bedding. This, however, cannot explain the discrepancy on the plus side and can answer only for a part of the minus divergence. We must look elsewhere for complete explanation. In the work on malaria,[10] it was demonstrated that the rectal temperature is a rather inaccurate measure of general body conditions. It may rise more rapidly or less rapidly than the average body temperature during sudden changes in heat elimination and production. In the calculation of the heat production by direct calorimetry the rectal temperature is assumed to represent accurately the temperature conditions of the whole body. This assumption is not valid during rapid fluctuations of temperature, but probably holds where the temperature rises and falls gradually as in the cases of erysipelas studied. In Figures 11 and 12 the curves of both rectal and average body temperature are charted. It will be seen that they are practically parallel.

One of the patients observed on the first day of normal temperature after the subsidence of fever exhibited a basal metabolism 8 per cent. below the average normal level. The other afebrile patient, also observed on the day following the crisis, still showed a heat production 12 per cent. above the normal. During the course of the fever, the metabolism was always high, the variations being between 19 and 42 per cent. above the average normal basal.

Relation of Basal Metbolism to Temperature.—In typhoid fever and tuberculosis [11] the increase in heat production was found to be roughly

10. Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Paper 28, The Metabolism in Malarial Fever, Arch. Int. Med. **21**:627 (May) 1918.

11. McCann, W. S., and Barr, D. P.: Clinical Calorimetry, Paper 29, The Metabolism of Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.

TABLE 1.—CALORIMETRIC—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Arshel A.	Prelim.	11:35	....	....	....	....	....	....	....
10/13/16	1	12:35	23.5	23.1	0.74	34.4	0.60	....	76.4
56.4 Kg. 1.58 Sq. M.	2	1:35	24.7	24.3	0.74	37.1	0.60	....	79.6
	Aver	.....	....	....	....	....	....	77.3	....
Arshel A.	Prelim.	6:47	....	....	....	....	....	....	....
40/15/16	1	7:47	25.2	23.5	0.78	39.9	0.49	....	83.5
55.6 Kg. 1.57 Sq. M.	2	8:47	24.0	24.0	0.73	35.8	0.49	....	81.5
	3	9:17	11.5	10.8	0.77	16.1	0.49	....	38.6
	4	10:47	36.3	35.1	0.75	50.2	0.49	....	125.0
	5	12:47	45.6	44.2	0.75	61.7	0.49	....	164.0
	6	2:47	43.5	43.6	0.73	61.6	0.49	....	163.9
	Aver.	.....	....	....	....	....	....	74.2	....
James W.	Prelim.	11:32	....	....	....	....	....	....	....
10/17/16	1	12:32	21.3	17.9	0.87	32.8	0.45	59.7	64.4
54.8 Kg. 1.67 Sq. M.	2	1:32	20.4	18.3	0.81	33.0	0.45	60.9	65.9
	Aver.	.....	....	....	....	....	....	....	....
Odysseo. B.	Prelim.	11:07	....	....	....	....	....	....	....
10/27/16	1	12:07	27.0	25.9	0.76	42.6	0.66	85.2	83.4
54.0 Kg. 1.59 Sq. M.	2	1:08	28.9	27.5	0.76	39.0	0.66	90.3	85.5
	Aver.	.....	....	....	....	....	....	....	....
Robert H.	Prelim.	11:24	....	....	....	....	....	....	....
11/1/16	1	12:24	28.3	27.4	0.75	43.5	0.65	80.6	98.5
60.0 Kg. 1.67 Sq. M.									
Robert H.	Prelim.	11:22	....	....	....	....	....	....	....
11/3/16	1	12:22	30.3	44.1	0.78	38.4	0.60	145.7	80.7
59.9 Kg. 1.67 Sq. M.	2	12:52	16.9			19.4	0.60		47.7
	3	1:22	15.4	14.9	0.75	13.9	0.60	49.0	43.3
	4	2:22	27.6	26.5	0.76	36.6	0.60	86.8	81.5
	5	3:22	29.7	27.8	0.78	39.8	0.60	91.6	90.9
	6	4:22	31.1	29.3	0.77	41.5	0.60	96.5	93.1
	Aver.	.....	....	....	....	....	....	93.9	....
Robert H.	Prelim.	12:11	....	....	....	....	....	....	....
11/5/16	1	1:11	29.1	28.6	0.74	37.2	0.73	93.9	100.0
60.4 Kg. 1.67 Sq. M.									
Robert H.	Prelim.	11:42	....	....	....	....	....	....	....
11/8/16	1	12:42	24.0	22.0	0.79	43.1	0.39	78.2	78.2
59.0 Kg. 1.67 Sq. M.	2	1:42	21.1	22.7	0.77	37.9	0.39	75.0	73.3
	Aver.	.....	....	....	....	....	....	....	....
Joseph S.	Prelim.	11:52	....	....	....	....	....	....	....
3/6/17	1	12:52	32.1	29.9	0.78	40.9	0.33	99.2	99.2
69.0 Kg. 1.81 Sq. M.									
Joseph S.	Prelim.	11:37	....	....	....	....	....	....	....
3/9/17	1	12:37	28.4	27.2	0.76	43.2	1.05	....	88.8
67.2 Kg. 1.81 Sq. M.	2	1:37	29.7	25.7	0.84	39.3	1.05	....	87.3
	Aver.	.....	....	....	....	....	....	96.9	....

—Data in Erysipelas

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	39.3	..	..	....	..	..	..	....	....	Basal
79.7	39.4	100	5	....	..	..	..	....	....	Very quiet
84.3	39.5	96	8	....	..	..	.	....	....	Very quiet
....	....	..	..	0.72	21	74	5	1.37	48.9	
....	40.0	..	..	....	..	..	..	....	....	Falling temperature
75.4	39.9	90	17	....	..	..	..	....	....	Very quiet, voided twice
78.0	39.8	..	12	....	..	..	..	....	....	Very quiet
37.4	39.8	..	2	....	..	..	..	....	....	Very quiet
107.8	39.4	85	..	....	..	..	..	....	....	Very quiet
148.6	39.1	..	14	....	..	..	..	....	....	Very quiet
151.2	38.9	80	8	....	..	..	..	....	....	Very quiet
....	....	..	..	0.73	17	75	8	1.33	47.3	
....	36.4	62	..	....	..	..	..	....	....	Basal
68.6	36.5	58	..	0.88	30	35	45	1.10	....	Slightly restless
64.6	36.5	58	..	0.81	30	51	29	1.11	....	Fairly quiet
....	....	..	..	....	..	..	..	....	30.6	
....	38.7	..	..	....	..	..	..	....	....	Basal
86.5	38.8	67	21	0.74	21	70	9	1.57	....	Fairly quiet
90.3	38.9	67	62(?)	0.75	20	68	12	1.65	....	Restless, coughing
....	....	..	..	....	..	..	..	....	54.6	
....	39.5	106	..	....	..	..	..	....	....	Basal
98.0	39.6	102	43	0.74	19	72	9	1.49	52.7	Somewhat restless
....	39.7	91	..	....	..	..	..	....	....	Rising temperature
105.1	40.2	91	20	0.77	..	..	..	1.63	....	Fairly quiet, shivering 12:10–1:10 p. m.
51.4	40.3	105	18							Slightly restless
46.0	40.3	..	16	0.74	..	..	..	1.64	....	Slightly restless
91.0	40.5	104	10	0.75	..	..	..	1.45	....	Quiet, sleeping
91.8	40.6	115	23	0.77	..	..	..	1.53	....	Fairly quiet
87.3	40.5	110	35	0.77	..	..	..	1.62	....	Slightly restless
....	....	..	..	....	17	66	17	....	56.2	
....	39.5	102	..	....	..	..	..	....	....	Basal
89.9	39.1	108	33	0.72	20	75	5	1.55	56.0	Restless
....	37.3	..	..	....	..	..	..	....	....	Basal
75.9	37.2	88	26	0.79	14	67	19	1.24	....	Slightly restless
75.3	37.2	78	17	0.77	14	68	18	1.27	....	Fairly quiet
....	....	..	..	....	..	..	..	....	44.3	
....	40.1	..	..	....	..	..	..	....	....	Basal
100.7	40.3	94	30	0.78	9	68	23	1.44	54.8	Rather restless
....	39.0	..	..	....	..	..	..	....	....	Basal
91.1	39.0	82	16	....	..	..	..	....	....	Fairly quiet dozed, 5 minutes
89.0	39.1	..	11	....	..	..	..	....	....	Quiet
....	....	..	..	0.79	22	48	30	1.29	48.0	

TABLE 2.—Summary of Results in Erysipelas

Subject	Date	Surface Area, Sq. M.	Stage of Disease	Rectal Temperature, C.	Length of Period	Average R. Q.	Heat Eliminated, Cal.	Heat Produced, Cal.	Per Cent. Divergence of Direct from Indirect	Average Calories per Sq. M. per Hour. Indirect	Rise Above Average Normal, Basal Linear	Per Cent. of Total Heat Elimination Lost in Vaporization of Water
Arshel A.	10/13/16	1.58	Febrile period, rising temperature	39.3-39.5	2 hours	0.74	156.0	164.0	+6.2	48.9	+23	26.8
Arshel A.	10/15/16	1.57	Febrile period, falling temperature	40.0-38.9	8 hours	0.75	656.5	508.4	+0.8	47.3	+19	23.6
James W.	10/17/16	1.67	First day, normal temperature	36.4-36.5	2 hours	0.84	129.4	133.3	+9.6	36.6	— 8	29.7
Odysseo B.	10/27/16	1.59	Febrile period, rising temperature	38.7-38.9	2 hours	0.76	168.9	176.8	+0.8	54.6	+38	28.2
Robert H.	11/ 1/16	1.67	Febrile period, high temperature	39.5-39.6	1 hour	0.75	93.5	98.0	+9.3	53.7	+35	27.2
Robert H.	11/ 3/16	1.67	Febrile period, rising temperature	39.7-40.6	5 hours	0.77	457.2	472.5	+0.6	56.2	+42	26.0
Robert H.	11/ 5/16	1.67	Febrile period	39.5-39.1	1 hour	0.74	100.0	80.9	—13.5	56.0	+41	33.4
Robert H.	11/ 8/16	1.67	First day of low temperature	37.3-37.2	2 hours	0.78	155.5	148.2	0	44.3	+12	30.6
Joseph S.	3/ 6/17	1.81	Febrile period, high temperature	40.1-40.3	1 hour	0.78	98.2	100.7	+1.4	54.8	+38	25.6
Joseph S.	3/ 9/17	1.81	Febrile period, high temperature	39.0-39.1	2 hours	0.80	176.1	180.1	+3.2	48.0	+20	27.4

proportional to the degree rise in rectal temperature. The same relation is found in erysipelas. Figure 6 expresses this relationship graphically according to the method used by McCann and Barr in tuberculosis. The abscissas show the level of metabolism in percentage of the average normal, the ordinates show the rectal temperature in degrees Centigrade. The line 90 means 10 per cent. below the average normal;

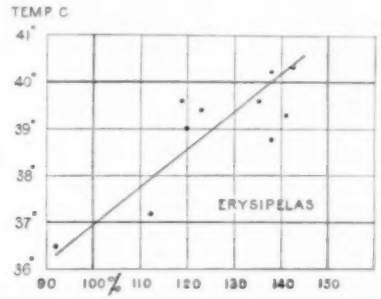

Fig. 6.—Relationship of basal metabolism to temperature in erysipelas. Ordinates represent rectal temperature in degrees Centrigrade; abscissae the metabolism expressed in percentages of the average normal. Each dot represents an experimental period in the calorimeter.

150 means 50 per cent. above the average. Each dot represents a calorimetric experiment. The diagonal line represents the average. Figure 7 expresses the same relation for the more numerous observations on typhoid fever. The heat production in typhoid increases a little more rapidly for each degree rise in temperature but on the whole the curves are strikingly similar.

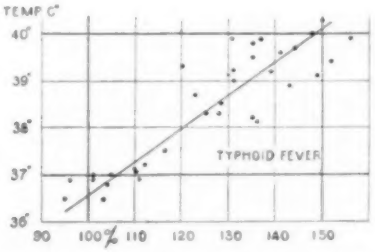

Fig. 7.—Relationship of basal metabolism to temperature in typhoid fever.

Nitrogen Equilibrium and Weight.—The observations on the nitrogen metabolism are disappointing and inconclusive. In spite of the determined efforts of a well trained staff of nurses, it was impossible to induce the patients to take nourishment sufficient for their caloric need during the fever. In figures 8, 9, and 10, the temperature, weight,

nitrogen intake and output together with the total food intake are represented graphically. The dashes of the dot dash line at the foot of the charts represent the heat production as calculated from actual observations in the calorimeter. The clinical data from which the charts are drawn will be found in Table 3. It will be seen that during the febrile course the expenditure of energy was always in excess of the caloric intake. No conclusions, therefore, may be drawn concerning toxic destruction of the body protein. Even normal individuals may show a nitrogen loss during an insufficient caloric intake.

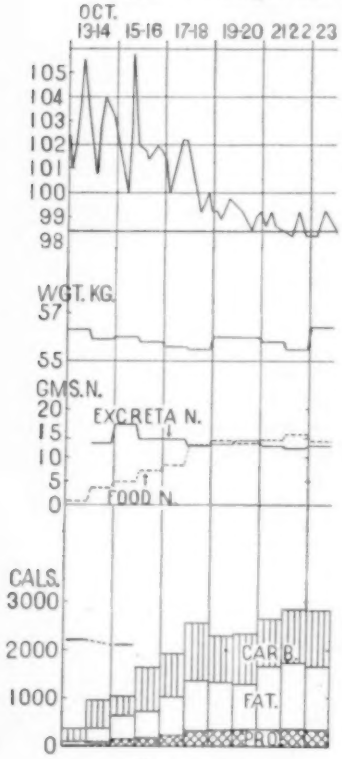

Figure 8

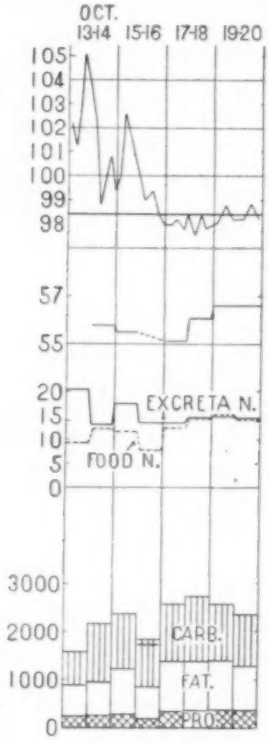

Figure 9

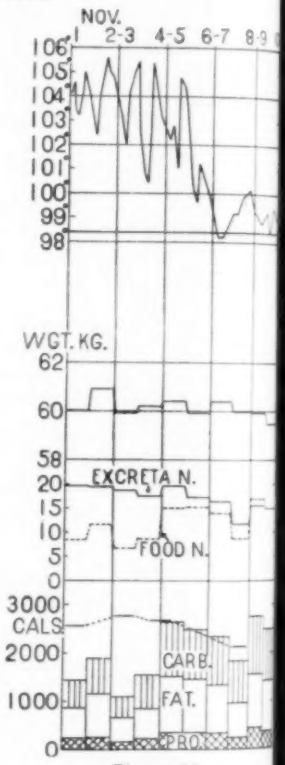

Figure 10

Fig. 8.—Arshel A. (Case 1) Temperature, body weight; food nitrogen dotted line; excreta nitrogen, continuous line. At the base of chart, columns representing total calories of food. The dot dash line represents the estimated heat production for twenty-four hours. The dashes are placed on days of the observations in the calorimeter.

Fig. 9.—James W. (Case 2) Temperature, body weight, food and excreta in nitrogen, food calories and dot dash line showing estimated heat production.

Fig. 10.—Robert H. (Case 4) Temperature, body weight, food and excreta nitrogen, food calories and dot dash line showing estimated heat production.

TABLE 3.—Clinical Calorimetric Data in Four Cases of Erysipelas

Name and Date	Body Weight	Food				Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	Nitrogen Balance, Gm.	Urine Volume, C.c.
		Total Calories	Carbohyd., Gm.	Fat, Gm.	Alc., Gm.					
James W.										
10/13/16	....	1,508	174	69	...	9.5	19.4	20.3	—10.8	1,730
10/14/16	55.8	2,196	278	84	...	10.6	12.2	13.3	— 2.7	1,560
10/15/16	55.5	2,368	273	100	...	12.0	16.5	17.7	— 5.7	1,640
10/16/16	....	1,832	236	71	...	8.9	13.1	13.9	— 5.9	1,355
10/17/16	55.1	2,645	301	116	...	12.7	12.4	13.7	— 1.0	1,800
10/18/16	56.2	2,741	317	114	...	14.7	13.3	14.8	— 0.1	1,980
10/19/16	56.6	2,573	271	115	...	15.3	13.5	15.0	+ 0.3	2,300
10/20/16	56.6	2,378	280	92	...	14.5	13.2	14.6	— 0.1	1,530
Arshel A.										
10/13/16	56.4	346	57†	10	...	0.9	13.9	14.0	—13.1	1,213
10/14/16	55.9	972	144	31	...	3.6	12.7	13.1	— 9.5	1,210
10/15/16	56.0	1,049	100	55	...	5.0	12.6	12.1	— 7.1	1,070*
10/16/16	....	1,630	218	58	...	7.2	13.4	14.1	— 6.9	2,380*
10/17/16	55.6	1,968	228	87	...	8.5	12.9	13.8	— 5.3	2,480
10/18/16	55.5	2,576	291	115	...	12.4	11.4	12.6	— 0.2	1,220
10/19/16	56.0	2,306 ?	239 ?	106 ?	...	13.4 ?	11.5	12.8	+ 1.6	2,300
10/20/16	56.0	2,333	252	104	...	13.0	12.4	13.7	— 0.7	2,370
10/21/16	....	2,656	236	144	...	13.7	12.4	13.7	± 0.0	2,800
10/22/16	55.5	2,863	272	47	...	14.7	11.6	13.1	+ 1.6	2,300
10/23/16	56.4	2,835	282	44	...	13.5	11.2	12.6	+ 0.9	2,230
Odysseo B.										
10/26/16	54.5	1,371	134	68	...	7.4	15.7	16.4	— 9.0	690
10/27/16	53.9	963	108	38	54	3.2	14.3	14.3	—11.1	676
10/28/16	54.1	2,475	187	127	162	14.4	14.9	16.3	— 1.9	830
10/29/16	54.0	2,493	239	117	54	14.7	12.4	13.6	+ 1.1	510
10/30/16	54.4	2,493	270	106	...	15.6	14.2	15.6	.....	1,090
10/31/16	55.4	2,116	192	105	...	13.7	13.6	15.0	— 1.3	1,180
Robert H.										
11/ 1/16	60.0	1,429	137	69	...	8.4	18.0	19.8	—11.4	2,125
11/ 2/16	60.9	1,896	176	96	...	10.6	17.7	19.5	— 8.9	1,930
11/ 3/16	59.8	1,109	105	54	...	6.5	17.1	18.8	—12.3	1,555
11/ 4/16	60.1	1,537	174	65	...	8.3	16.0	17.6	— 8.3	1,380
11/ 6/16	60.3	2,656	282	119	...	15.1	18.1	19.9	— 4.8	2,980
11/ 6/16	59.9	2,515	257	115	...	15.1	15.6	17.2	— 2.1	1,120
11/ 7/16	60.3	2,339	241	106	...	14.0	15.2	16.7	— 2.7	2,570
11/ 8/16	59.1	1,861	216	80	...	8.8	10.7	11.8	— 3.0	1,477
11/ 9/16	59.8	2,775	292	121	...	17.0	14.2	15.6	+ 1.4	1,230
11/10/16	59.5	2,496	258	112	...	15.2	13.6	15.0	+ 0.2	1,640

* Excreta nitrogen estimated as urine nitrogen plus 10 per cent. of food nitrogen.
† Approximate.

The weight curves are of some interest. In studying pneumonia, Sandelowsky [12] found that, during the acute febrile course of the disease, many patients maintained their weight or even gained a considerable amount. At the crisis and during the early convalescence, on the other hand, there was a rapid loss in weight. This, he attributed to a storage of water in the body during fever and a rapid loss of water following it. He supported this hypothesis with refractometric studies of the serum proteins by which he demonstrated to his own satisfaction that there was a dilution of blood during the fever and a concentration or return to normal following it. In the light of Sandelowsky's contention, the weight curves in erysipelas are significant. During the acute course of the fever, it is a little surprising that the weight remains practically constant in spite of the insufficient food. At the crisis,

12. Sandelowsky, J.: Blutkonzentration bei Pneumonie, Deutsch. Arch. f. klin. Med. **96**:445, 1909.

and in convalescence, however, the fall of weight noted by Sandelowsky in pneumonia is not observed.

Regulation of Body Temperature.—In the chills of malarial fever,[9] it was found that the sharply rising temperature was accomplished by a great increase in the production of heat while the elimination of heat remained at the level which had existed before the chill. Following the paroxysm there was a period of high continuous temperature. In this stage, the heat production fell while the heat elimination increased until the two were equal to each other. Both, however,

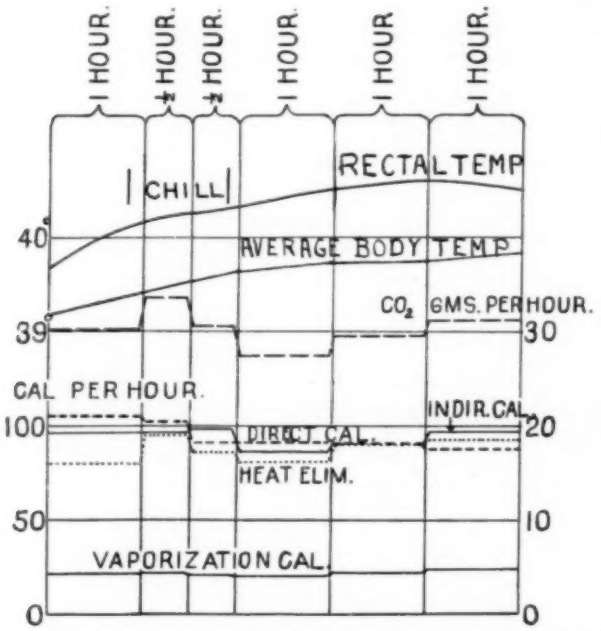

Fig. 11.—Metabolism chart. Robert H (Case 4) curves showing relationship of heat production to heat elimination.

were maintained at a level high above the normal basal metabolism. The conditions under which the erysipelas patients were studied may be considered analogous to the high constant temperature following the malarial paroxysm. Both heat production and elimination are at a high level, which, as we have seen, varies with the degree of fever. In erysipelas, however, the temperature is seldom truly continuous. There are usually frequent remissions, sometimes intermissions. It would be interesting to know how these fluctuations are brought about and whether the mechanism of the rise and fall of temperature during

a high fever is similar to that of malaria in which the temperature is originally normal. It was with these questions in mind that the study of erysipelas was undertaken. Unfortunately our data are not sufficient to answer them. Only two long observations were made during significant changes in temperature. In both, the changes were so gradual that it is impossible to draw conclusions from them. Figure 11 represents graphically the results of studies made on Robert H. during a rising temperature while Figure 12 shows in a similar manner the results of studies made on Arshel A. during a falling temperature. It is interesting to note that the rather sharp rise during the first two

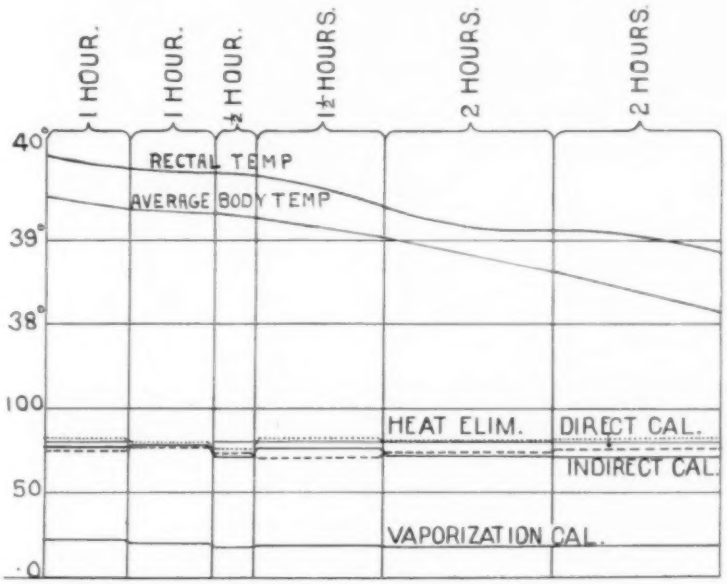

Fig. 12.—Metabolism chart. Arshel A. (Case 1) curves showing relationship of heat prouction to heat elimination.

hours of the observation on Robert H. was accompanied by shivering which amounted to a moderate chill. During these periods, the heat production was high. After the shivering ceased, the production of heat diminished while the heat elimination increased in a manner quite comparable with that observed in malaria. During the falling temperature shown in Figure 12, the heat elimination remained at a practically constant level throughout the seven and a half hours of the observation. The heat production gradually fell.

Heat Loss by Vaporization of Water.—The question of water utilization in fever is of great importance. Because of its ability to

absorb heat and its fluid character water offers the chief means of carrying heat from the cells where it is produced to the surface of the body where it may be eliminated. Heat loss both through radiation and conduction and through vaporization is therefore dependent on the proper mobilization of water within the body. Because of the dry skin, concentrated urine and other phenomena of fever, it has been argued that the water supply of the body is depleted or cannot be mobilized. This has been considered a possible cause of fever by Balcar, Sansum and Woodyatt.[13] Facts concerning the heat lost in vaporization of water from skin and lungs are relevant to this question.

Under the constant temperature conditions of the calorimeter, normal subjects accomplish about 24 per cent. of their total heat elimination by vaporization of water. The average percentage was slightly lower, about 22 per cent. in typhoid fever. In erysipelas, on the other hand, the heat lost in the vaporization of water is high in proportion to the total elimination. During the rising temperature observed in Robert H. (Fig. 11), it constituted 26 per cent. The limits of variation for all the observations were from 23.6 to 33.4 per cent.

SUMMARY AND CONCLUSIONS

1. Ten calorimetric experiments have been made in five cases of erysipelas. Two of these were taken on the day following the crisis. The others were made during the febrile course of the disease.

2. During the fever, the metabolism is increased from 19 to 42 per cent. above the average normal basal. The increase in metabolism is roughly proportional to the degree of fever. A temperature of 40 C. involves a heat production of about 40 per cent. above the average normal.

3. The change in rectal temperature is not always an accurate index of the change in average body temperature in erysipelas

4. The regulation of body temperature is similar to that observed in malaria during the stage of high continuous temperature. Both heat production and heat elimination are maintained at a high level.

5. The heat lost in the vaporization of water constitutes from 23.6 to 33.4 per cent. of the total heat elimination. During rising, constant and falling temperatures the percentge of heat eliminated in the vaporization of water was greater than in normal individuals.

6. No specific differences were found between the metabolism in erysipelas and in typhoid fever. Both fevers show approximately the same increases in the level of heat production for the same increase in body temperature. The protein metabolism is greatly increased in both diseases.

---

13. Balcar, J. B.; Sansum, W. D., and Woodyatt, R. F.: Fever and Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

CLINICAL CALORIMETRY. XXXI. OBSERVATIONS ON THE METABOLISM OF ARTHRITIS *

RUSSELL L. CECIL, M.D.; DAVID P. BARR, M.D.,
AND
EUGENE F. DU BOIS, M.D.
WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM AND ESTELLE MAGILL
NEW YORK

In recent years, bacteriologists have made important contributions to the etiology of arthritis, especially in regard to the part played by focal infections. The large mass of evidence which has gradually accumulated indicates that most cases of arthritis are infectious in origin. In spite of this, however, some practitioners have held to the belief that arthritis, particularly in its chronic form, is an expression of a disturbance in metabolism. The relationship between gouty arthritis and an abnormal purin metabolism gave some ground for this theory, and for many years the various forms of acute and chronic arthritis were supposed to be dependent on the retention in the body of uric acid or some kindred substance. For this reason rheumatic patients were often put on a reduced nitrogenous diet, but the results obtained by this mode of treatment were not encouraging. Pemberton [1] has advocated a lowered carbohydrate intake for arthritis patients.

Comparatively little experimental work was done on the metabolism of arthritis before the extensive studies of Pemberton and his associates [2] published in 1920. Indeed, it is only within the last few years that the development of newer and more accurate methods in biochemistry have made reliable investigations along this line possible. Tileston and Comfort,[3] who studied the nonprotein nitrogen and urea in the

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Pemberton, R.: The Metabolism and Treatment of Rheumatoid Arthritis, Fourth Paper, Am. J. M. Sc. **153**:678, 1917.

2. Pemberton, R., and Robertson, J. W.: Studies on Arthritis in the Army, Based on Four Hundred Cases. I. Preamble and Statistical Analysis, Arch. Int. Med. **25**:231 (March) 1920. Pemberton, R., and Tompkins, E. H.: Ibid. II. Observations on the Basal Metabolism, Arch. Int. Med. **25**:241 (March) 1920. Pemberton, R., and Foster, G. L.: Ibid. III. Studies on the Nitrogen, Urea, Carbon Dioxid Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood Renal Function, Blood Sugar and Sugar Tolerance, Arch. Int. Med. **25**:243 (March) 1920. Pemberton, R., and Buckman, T. E.: Ibid. IV. Studies in the Relation of Creatin Metabolism to Arthritis, Arch. Int. Med. **25**:335 (April) 1920. Pemberton, R.: Ibid. V. Roentgen-Ray Evidences, Clinical Considerations, Treatment, Summary, Conclusions and Clinical Abstracts of Cases Studied, Arch. Int. Med. **25**:351 (April) 1920.

3. Tileston, W., and Comfort, C. W., Jr.: The Total Nonprotein Nitrogen and the Urea of the Blood in Health and Disease, as Estimated by Folin's Methods, Arch. Int. Med. **14**:620 (Nov.) 1914.

blood in various diseases, obtained low figures in rheumatic fever. Pemberton and Foster [2] estimated the blood urea and nonprotein nitrogen in seventeen cases of chronic arthritis and found that the figures in every case were well within the normal limits. Pemberton and Buckman [3] made determinations of the nonprotein nitrogen in the blood in forty cases of arthritis and found an abnormal elevation in only two cases. Folin and Denis [4] found an increase of uric acid in the blood in nongouty arthritis. Similar results were obtained by McClure and Pratt.[5] Pemberton and Buckman [3] carried out observations on the creatin and creatinin of the blood and urine in forty cases of arthritis. About one-half of the cases showed an abnormally high value for blood creatinin. Pemberton and Foster [2] also estimated the carbon dioxid combining power of the blood, the calcium of the circulating blood and the total fat and cholesterol of the fasting blood. In all cases the figures were well within normal limits. These authors did find evidence of an abnormal rise in the blood sugar following the ingestion of 100 gm. glucose.

Pemberton and Tompkins [2] studied the basal metabolism in a series of twenty-nine cases of arthritis, the observations being made by indirect calorimetry, using the Tissot apparatus. Of the cases studied, 80 per cent. showed a metabolism within normal limits, in 20 per cent. the rate was slightly below normal limits. From the respiratory quotients no abnormality could be detected in the percentage of calories obtained from the three classes of foodstuffs.

The present investigation, carried out in 1916-1917, deals with the metabolism in two cases of acute arthritis, two cases of subacute arthritis, one case of gouty arthritis and four cases of chronic arthritis. Circumstances prevented the study of a larger series but it seemed desirable to publish the data at hand in order to complement the report of Pemberton and Tompkins and to render the records accessible to future workers.

METHODS

The experiments reported in this study were carried out on patients in Bellevue Hospital. The calorimeter of the Russell Sage Institute of Pathology was employed. The heat production was measured by both the direct and indirect methods. The actual details of technic have been described fully in previous articles in this series.[6]

The basal metabolism of four cases of acute and subacute arthritis was determined. Edward C. (Case 1) had a typical case of acute

4. Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Determinations in Blood, Arch. Int. Med. **16**:33 (July) 1915.

5. McClure, C. W., and Pratt, J. H.: A Study of Uric Acid in Gout, Arch. Int. Med. **20**:481 (May) 1917.

6. Clinical Calorimetry, Arch. Int. Med. **15**:793-945 (May) 1915; **17**:855-1059 (June) 1916; **19**:823-957 (May) 1917.

rheumatic fever. John Bl. (Case 2) was considered to have subacute rheumatic fever. John Br. (Case 3) had acute arthritis associated with gonorrheal urethritis and a conjunctivitis of gonococcus origin. Joseph McC. (Case 4) had a subacute arthritis and an intermittent urethral discharge of several years duration. Observations concerning the nitrogen equilibrium were made on one patient, John Br. (Case 3).

REPORT OF CASES

CASE 1.—Acute Rheumatic Fever.

History.—Edward C., a waiter, born in Ireland, 33 years of age, was admitted, Jan. 13, 1917, and discharged unimproved, Jan. 29, 1917. Since childhood he has had frequent attacks of severe sore throat, and he has had quinsy four times. In 1906, he had symptoms of scarlet fever and was treated at a contagious hospital. During the course of the disease, he developed a very severe joint attack which lasted two weeks. In July, 1912, he was operated on for appendicitis, and in November, 1912, he was operated on for ulcer of the stomach. He was kept on a diet for one year after the operation. He was a convivial drinker, but denied venereal disease.

November 24 an operation was performed on his nose. Following this he had a severe hemorrhage from the nose lasting four hours. November 29 he was seized with a severe quinsy which was lanced December 1. He rapidly recovered from the throat trouble, but December 20 he was seized with pain in the muscles and joints which remained severe for about a week. Vague pains were present until January 13 when they again became very severe.

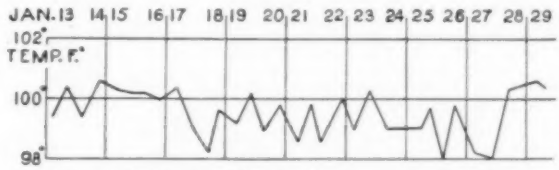

Fig. 1.—Edward C. (Case 1). Temperature Chart.

Physical Examination.—The patient was a rather pallid, poorly nourished young Irishman of cheerful disposition. The tonsils were much enlarged, the right being larger than the left. The crypts are deep but there are no follicles present. The teeth are in fair condition.

Heart: The left border of dulness in the fifth space is 11.5 cm. from the median line; the right border is beneath the sternum. There is a definite, short, soft systolic murmur, heard best at the apex, transmitted to the mid-axilla and the sternum.

Abdomen: Shows scars of previous operations. Rectal examination disclosed a normal prostate and seminal vesicles. There was some pain, on motion, in both shoulders, but no swelling or redness.

Laboratory Examination.—Urine: Moderate trace of albumin; no casts. Blood pressure: Systolic, 140 mm.; diastolic, 85 mm. Blood cultures: Negative. Tonsil cultures: *Streptococcus viridans* (blood agar plates); from right tonsil, *S. viridans* and a moderate number of *Staphylococcus aureus* colonies and a diphtheroid bacillus from the left tonsil. Wassermann test: Negative. Gonococcus fixation test: Negative.

January 22 he was in the calorimeter from 10:50 a. m. to 1:50 p. m. He had moderate pain in both shoulders, in the right wrist and in both knees. None of the joints showed swelling, tenderness or redness. This condition was practically unchanged when he was discharged January 29.

Case 2.—Subacute Rheumatic Fever.

History.—John Bl., a bookkeeper, born in Scotland, 58 years of age, was admitted Jan. 22, 1917, and discharged cured Feb. 7, 1917. In 1914 he had an attack of joint pain similar to the present one. He had pneumonia in 1912. Thirty years ago he had gonorrhea without complications. He drinks one glass of whiskey and three glasses of beer daily but is rarely intoxicated. His father died of "rheumatism and heart trouble."

January 8 he began to have vague pains in the muscles. January 18, following exposure to the weather, both knees became very painful and swollen. He felt chilly during the day and was nauseated. Two days later his ankles began to swell, and finally his arms and hands became stiff and swollen.

Physical Examination.—The patient was a large, robust Scotchman, not very ill. The tongue showed a moderate white coat. The tonsils were atrophic but red with chronic congestion. Most of the teeth were missing, although there was no definite pyorrhea. Heart: Not affected. Lungs: Show signs of a moderate emphysema. At the right base are many coarse, leathery friction rubs and diminished breathing. There was swelling and exquisite tenderness of the right and left knee joints; wrists and, to a lesser extent, of the ankles. On the right shin is the scar of an old varicose ulcer.

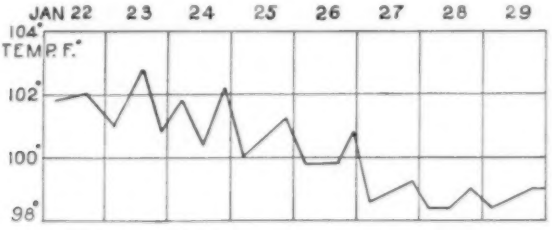

Fig. 2.—John Bl. (Case 2). Temperature Chart.

Laboratory Examination.—Urine: Negative. Blood pressure: Systolic, 130 mm.; diastolic, 90 mm. Blood culture: Negative. Blood: Leukocytes, 12,000; polymorphonuclears, 80 per cent.; hemoglobin, 80 per cent. Wassermann test: Negative. Gonococcus fixation test: Negative. Culture of each tonsil shows abundant and almost pure growth of *Streptococcus viridans* and a few colonies of *Staphylococcus aureus.*

January 26, from 10:45 a. m. to 1:45 p. m., he was in the calorimeter. At that time the hands, wrists and knees were moderately hot and swollen. The elbows and shoulders were tender and painful on motion. The joints improved gradually and he was discharged as cured February 7.

Case 3.—Acute Gonococcus Arthritis.

History.—John Br., a clerk, born in the United States, 19 years of age, was admitted Jan. 25, 1917, and discharged improved March 23. Both his mother and his father had rheumatism. The mother died in 1916 of chronic alcoholism. He had chorea in early childhood. He says that between the ages of 5 and 13 he averaged one attack of "rheumatism" a year, but has had none since. The attacks were usually mild and did not force him to go to bed. He never had tonsillitis.

January 7, seven days after intercourse, he began to have a urethral discharge. January 13 he had severe pains in the right knee. Later, the right foot, left foot and right thumb were affected. Pains became very severe and motion was limited.

Physical Examination.—The patient was a well developed, somewhat emaciated boy, acutely ill, rather toxic. The tongue was slightly dry with a brown coat. The eyes showed a moderately severe conjunctivitis. The tonsils were small with deep crypts and no signs of inflammation. The heart was not involved. The left knee joint was distended with fluid, hot, slightly tender and held in semiflexion. Considerable motion was possible without great pain. The right knee showed signs of inflammation and contained some fluid. Both ankles were swollen, the left more than the right. There was marked tenderness

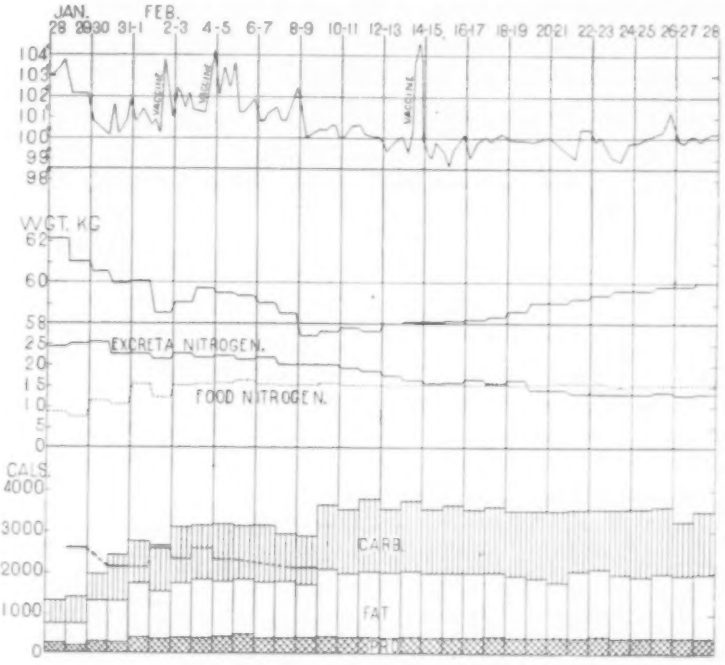

Fig. 3.—John Br. (Case 3). Acute arthritis, gonococcus origin. Temperature, body weight; excreta nitrogen, continuous line; food nitrogen, dotted line. At base of figure, columns representing total calories of food. The dot dash line represents the estimated heat production in calories for twenty-four hours. The dashes are placed on days of the observations in the calorimeter. Note that the calories of the food exceed the estimated heat production except for the first two days of observation.

over the tarsometatarsal joints of both feet; tenderness and pain on motion in the metatarsophalangeal joint of the great toe and of the metacarpophalangeal joint of the thumb. There was a moderate, white, purulent urethral discharge containing gonococci in large numbers. The prostate was not enlarged. The urine from the posterior urethra was clear and contained only an occasional pus cell. The urine from the anterior urethra contained many pus cells but no albumin or casts.

Laboratory Examination.—Blood: February 2 (before vaccine), leukocytes 11,000; polymorphonuclears, 75 per cent. Blood culture: January 30 and February 3, sterile. Wassermann negative. Gonococcus fixation test: January 26, doubtful; January 31, negative. Tonsil culture, February 3: Both tonsils showed *Streptococcus viridans* predominant but with scattering colonies of *Staphylococcus aureus* and *Micrococcus paratetragenus.*

January 29 he was in the calorimeter from 11 a. m. to 3 p. m.; January 31, from 10:30 a. m. to 2:10 p. m. February 2 a faint presystolic murmur was heard for the first time, just medial to the apex of the heart. On the same day, at 10:50 a. m. he was given intravenously a 25 million dose of the New York Board of Health typhoid vaccine and was observed in the calorimeter from 11 a. m. to 3:15 p. m. February 4 he received a second dose of typhoid vaccine. February 5, 10 c.c. of cloudy fluid was removed from the left knee joint. The smear showed large numbers of polymorphonuclear cells and a few endothelial cells. Occasional gram-negative intracellular bodies, resembling gonococci, were seen. The cultures were negative on ascitic glucose agar plate, deep ascitic glucose agar tube, blood broth, ascitic and plain broth. February 9, from 11 a. m. to 2:15 p. m., he was in the calorimeter. February 14 he received a third injection of typhoid vaccine. He remained in the metabolism ward until March 1 when he was discharged to the general service.

January 29 he weighed 137 pounds; February 9, 126 pounds; March 1, 131 pounds. During the time of observation none of the joints originally affected were cured. There was frequently marked improvement with equally frequent relapse, sometimes following the administration of typhoid vaccine by twenty-four hours, sometimes by thirty-six hours, more frequently occurring spontaneously without reference to treatment. During the last three weeks, however, there was a very slow, general tendency to improvement. The heart murmur, which was first heard February 2, became much louder by February 9. March 1 it was again very feeble and March 5 it could be heard only after exercise. During the month the right side of the heart increased moderately in size. The electrocardiogram taken March 2 showed well marked right sided enlargement. The urethral discharge lessened with local treatment but never disappeared entirely. It remained localized to the anterior urethra.

In the general ward, from March 3 to 13, he received gonococcus vaccine intravenously in doses of from 20 to 30 million. His improvement was remarkable. The temperature, which had been continually elevated since entrance to the hospital, became normal and remained so except during the reactions following vaccinations. The pain disappeared. A moderate amount of fluid in the knee joints, however, remained unabsorbed. He received bakes and massage until March 23, when he was discharged. Both knee joints contained small amounts of fluid but there were no other symptoms. He was seen again in April. His right knee still contained a small amount of fluid but he was otherwise in excellent health.

Case 4.—Subacute Gonorrheal Arthritis.

History.—Joseph McC., an elevator operator, born in the United States, 27 years of age, was admitted Jan. 14, 1917, and discharged unimproved March 1, 1917. In 1910 he had an attack of gonorrheal urethritis followed by epididymitis. Since then he has had a urethral discharge several times, the last in November, 1916. In 1912 he had an acute arthritis involving all the joints, and he was ill for nine weeks. A second attack of the same character, in 1914, lasted two months. He has never had sore throat, chorea or other manifestations of acute rheumatic fever.

Jan. 3, 1917, he began to have a dull pain in the lower end of the spine and in the lumbosacral muscles, which radiated down the right thigh. His right heel became so painful that he could not walk. About the same time the urethral discharge recommenced.

Physical Examination.—This shows an undeveloped, poorly nourished man. He held himself very stiff because of pain in the back. There was pain on pressure over the sacrococcygeal joint and marked tenderness over the spine of the ninth dorsal vertebra. The under surface of the right heel was exquisitely tender. There was a considerable watery, purulent urethral discharge, a smear of which showed gonococci. The prostate was moderately enlarged. The right seminal vesicle was palpable.

Laboratory Examination.—Urine from both anterior and posterior urethra contained pus but no albumin or casts. Gonococcus fixation test was negative. Wassermann reaction was negative. The roentgenogram showed periosteal exostosis of the os calcis of both heels.

His symptoms remained unchanged during the first seven days in the hospital. February 1 he was given intravenously 40 million of the New York City Board of Health typhoid vaccine. February 3, 5 and 7 similar doses were given. The character of the reactions following the injections appears on the temperature chart. The chills began from thirty to seventy-five minutes after injection. February 13 a dose of 50 million was given.

February 7 and 13 the patient was observed in the calorimeter. No noticeable improvement resulted from the vaccine therapy. On the first day following each injection he was more stiff and uncomfortable. On the second day the condition returned to that which obtained before the vaccine was given. Except at the times when he was given vaccine this patient had a normal temperature.

Results of the study of basal metabolism in the cases of acute and subacute arthritis will be found in the summary, Table 4, the detailed calorimeter data in Table 1.

It will be noted that the patients studied showed but slight elevation in the basal metabolism as measured by the surface area standards of Aub and Du Bois. All but one determination came within 12 per cent. of the average normal figure. This single exception was found in the case of John Br. who showed a basal metabolism 26 per cent. above the average normal when he was slightly restless with a constant temperature of 38.4 C. This case deserves mention from another standpoint.

In Figure 3 and Table 2, it will be seen that during the period of high temperature, 100-104 F., there was a persistent negative nitrogen balance similar to that observed by Coleman and Du Bois[7] in typhoid fever. This occurred during a time when he was receiving a well balanced ration greatly in excess of his heat production as measured by several calorimeter observations. This phenomenon was so distinctly abnormal that it is necessary to assume a toxic destruction of body protein caused by the gonorrheal arthritis. Since this negative nitrogen balance continued during a period when the temperature was comparatively low, it is natural to infer that the destruction of protein was due to toxins rather than the hyperpyrexia.

7. Coleman and Du Bois: Clinical Calorimetry. Paper 7.—Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food. Arch. Int. Med. **15**:882 (May) 1915.

TABLE 1.—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
William B.	Prelim.	12:14	....	....	....	....	....	....	....
12/6/16									
63.7 Kg.	1	1:14	26.2	24.2	0.79	31.1	0.39	80.2	78.6
1.80 Sq. M.	2	2:18	28.9	25.3	0.83	35.1	0.49	84.7	82.6
	Aver.	.....	....	....	....	....	....	80.0*	....
William B.	Prelim.	11:50	....	....	....	....	....	....	....
12/11/16									
63.6 Kg.	1	12:50	23.9	21.3	0.82	28.3	0.48	....	77.0
1.80 Sq. M.	2	1:50	24.2	22.2	0.79	29.8	0.48	....	76.4
	Aver.	.....	....	....	....	....	....	72.0	....
William B.	Prelim.	11:57	....	....	....	....	....	....	....
12/8/16									
63.6 Kg.	1	12:57	27.6	21.5	0.93	31.7	0.58	73.7	75.0
1.80 Sq. M.	2	1:57	28.8	21.8	0.96	31.7	0.58	74.9	75.6
	3	2:59	33.0	24.5	0.98	37.0	0.58	82.3	84.6
William B.	Prelim.	11:16	....	....	....	....	....	....	....
12/13/16									
64.3 Kg.	1	12:17	30.7	24.1	0.93	35.7	1.00	79.7	84.2
1.80 Sq. M.	2	1:16	31.8	28.4	0.81	46.8	1.00	92.6	91.9
	3	2:16	33.9	29.6	0.84	55.2	1.00	96.9	99.8
	4	3:16	32.9	29.5	0.81	58.2	2.24	96.0	102.0
Edward R.	Prelim.	12:06	....	....	....	....	....	....	....
1/3/17									
37.8 Kg.	1	1:06	15.7	14.8	0.77	23.5	0.12	....	48.4
1.42 Sq. M.	2	2:06	15.8	14.5	0.79	21.7	0.12	....	49.1
	Aver.	.....	....	....	....	....	....	48.8	....
Edward R.	Prelim.	12:19	....	....	....	....	....	....	....
1/9/17									
38.8 Kg.	1	1:19	23.7	16.8	1.03	34.7	0.09	59.1	57.9
1.42 Sq. M.									
	2	1:59	....	....	....	....	....	....	....
	3	2:59	25.2	19.0	0.97	40.9	0.94	66.4	66.6
Edward McK.	Prelim.	12:03	....	....	....	....	....	....	....
1/5/17									
38.0 Kg.	1	1:03	19.3	17.0	0.82	23.8	0.10	....	56.7
1.37 Sq. M.	2	2:03	20.0	17.4	0.84	24.2	0.10	....	58.2
	Aver.	.....	....	....	....	....	....	58.1	....
Edward C.	Prelim.	11:52	....	....	....	....	....	....	....
1/22/17									
51.7 Kg.	1	12:52	21.1	20.1	0.77	33.1	0.43	....	70.7
1.56 Sq. M.	2	1:52	20.1	19.4	0.75	30.2	0.43	....	68.7
	Aver.	.....	....	....	....	....	....	64.4	....
John Bl.	Prelim.	11:46	....	....	....	....	....	....	....
1/20/17									
80.4 Kg.	1	12:46	26.8	25.7	0.76	33.4	0.63	....	76.9
2.01 Sq. M.	2	1:46	26.9	26.0	0.75	34.7	0.63	....	83.2
	Aver.	.....	....	....	....	....	....	84.7	....
John Br.	Prelim.	11:58	....	....	....	....	....	....	....
1/29/17									
61.2 Kg.	1	12:58	30.6	29.3	0.76	42.3	0.93	95.6	94.0
1.80 Sq. M.	2	1:58	30.2	28.3	0.78	40.6	0.93	92.8	93.8
	3	2:58	30.6	29.2	0.76	41.9	0.93	95.3	96.0
	Aver.	.....	....	....	....	....	....	....	....

* Average calories per hour.

—Calorimeter Data

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Ctm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	37.1	..	..	....	..	..	..	....	....	In chair
81.7	37.2	60	16	....	..	..	..	....	44.6	Apparently quiet, patient says he exercised fingers constantly
82.4	37.2	64	28	....	..	..	..	....	44.1	Second period prolonged because of falling barometer
....	....	..	..	0.81	16	55	29	1.26	44.4	
....	37.0	..	..	....	..	..	..	....	....	Basal, in chair
76.6	37.0	60	11	....	..	..	..	....	....	Quiet
82.4	37.1	64	20	....	..	..	..	....	....	Quiet, voided
....	....	..	..	0.81	18	53	29	1.13	40.0	
....	37.2	..	..	....	.	..	..	....	....	Dextrose 212 gm., 10:56–11:07 a. m.
69.9	37.1	65	17	0.96	16	12	72	1.16	40.9	Quiet, asleep 15 min.
76.3	37.1	64	21	0.99	16	2	82	1.18	41.6	Quiet
85.1	37.2	74	21	1.01	16	0	84	1.25	44.3	Quiet
....	37.6	68	..	....	..	..	..	....	....	Chopped beef, 662 gm. (24.3 gm. N)
76.8	37.4	..	22	1.03	..	..	..	1.25	44.3	Moderately quiet
90.9	37.4	68	26	0.82	28	44	28	1.48	53.0	Moderately quiet
98.7	37.4	..	24	0.85	27	38	35	1.53	54.6	Quiet
101.4	37.5	69	21	0.82	02	23	15	1.48	52.9	Quiet
....	36.9	..	..	....	..	..	..	....	....	Basal
47.9	36.9	90	6	....	..	..	..	....	....	Very quiet
49.6	36.9	..	12	....	..	..	..	....	....	Very quiet
....	....	..	..	0.78	7	70	23	1.29	34.4	
....	37.2	..	..	....	..	..	..	....	....	Dextrose, 212 gm., 10:19 a. m.
57.3	37.2	..	3	1.04	4	0	96	1.52	41.8	Very quiet, pain; uncomfortable at start of second period
....	37.1	145	..	....	..	..	..	....	....	Removed from calorimeter, pillows shifted
63.0	37.0	..	6	0.97	3	10	87	1.71	46.7	Very quiet, pain
....	36.9	57	..	....	..	..	..	....	....	Basal
52.4	36.7	..	12	....	..	..	..	....	....	Fairly quiet
57.6	36.7	82	2	....	..	..	..	....	....	Very quiet
....	....	..	..	0.83	4	55	41	1.53	42.4	
....	37.4	..	..	....	.	..	.	....	....	Basal
60.5	37.2	76	22	....	..	..	..	....	....	Somewhat restless
71.0	37.3	..	13	....	..	..	..	....	....	Quiet
....	....	..	..	0.75	19	68	13	1.25	41.3	
....	37.7	..	..	....	..	..	..	....	....	Basal
73.9	37.6	80	6	....	..	..	..	....	....	Very quiet
81.5	37.6	..	4	....	..	..	..	....	....	Very quiet
....	....	..	..	0.74	20	70	10	1.05	42.2	
....	38.4	92	..	....	..	..	..	....	....	Basal
89.9	38.4	87	21	0.75	26	64	10	1.57	....	Restless, voiding
95.9	38.4	84	14	0.76	27	59	14	1.52	....	Fairly quiet
96.0	38.4	90	18	0.75	26	63	11	1.56	....	Fairly quiet
....	....	..	..	....	..	.	..	....	52.6	

TABLE 1.—CALORIMETER—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
John Br.	Prelim.	11:58	....	....	....	....	....	....	....
1/31/17									
59.7 Kg.	1	12:58	26.4	25.1	0.76	47.0	0.72	....	87.8
1.78 (Ht.-Wt.)	2	1:58	26.8	24.0	0.81	35.2	0.72	....	81.9
	Aver.	.....	....	....	....	....	....	80.8	....
John Br.	Prelim.	11:51	....	....	....	....	....	....	....
2/9/17									
57.4 Kg.	1	12:47	25.2	22.6	0.81	28.2	0.57	....	73.9
1.74 (Ht.-Wt.)	2	1:51	28.6	25.6	0.81	32.2	0.57	....	88.5
	Aver.	.....	....	....	....	....	....	80.2	....
Timothy S.	Prelim.	12:12	....	....	....	....	....	....	....
4/26/17									
53.4 Kg.	1	1:12	26.1	24.0	0.79	31.2	0.57	....	78.7
1.64 Sq. M.	2	2:12	26.1	24.2	0.79	30.2	0.57	....	78.1
	Aver.	*.....	....	....	....	....	....	79.5	....
Timothy S.	Prelim.	11:33	....	....	....	....	....	....	....
4/27/17									
53.4 Kg.	1	12:33	23.6	21.1	0.82	28.6	0.62	....	69.2
1.64 Sq. M.	2	1:33	24.0	21.5	0.81	27.7	0.62	....	70.1
	Aver.	.....	....	....	....	....	....	70.6	....
Timothy S.	Prelim.	11:06	....	....	....	....	....	....	....
5/12/17									
52.4 Kg.	1	12:06	21.9	18.1	0.88	25.7	0.53	....	61.0
1.64 Sq. M.	2	1:06	23.2	20.3	0.83	25.8	0.53	....	65.0
	Aver.	.....	....	....	....	....	....	64.3	....
Joseph McC.	Prelim.	11:09	....	....					
2/7/17, 51.4 Kg.					0.82	27.8	0.27	62.4	61.5
1.46 Sq. M.	1	12:09	20.9	18.6	....	....	....	....	....

* Average calories per hour.

METABOLISM IN GOUT

The basal metabolism in one case of gout was determined.

CASE 5.—

History.—Timothy S., a laborer, born in Ireland, 42 years of age, was admitted April 21, 1917, and discharged improved May 12, 1917. He has never had any serious illness and says that he is not alcoholic. Attacks of gout began in 1905 when he was 30 years of age. The first attack involved both great toes. Since that time the attacks have occurred at intervals of from two months to one year. The toes, knees and fingers have been involved. The present attack involved both knees and the small joint of the right hand.

Physical Examination.—The patient was a moderately emaciated, fairly well developed man. The pinnae of both ears showed large and small tophi. There were small tophaceous spots in the ear drum. The throat was moderately congested. The heart was not enlarged. Blood pressure: Systolic, 155 mm.; diastolic, 105 mm. The arteries were palpable but not sclerosed. The metacarpophalangeal joints of the thumb and the first three fingers of the right hand were tender, swollen and painful on motion. The right wrist and elbow were slightly involved. The left hand showed marks of deformity but no active

—DATA—(*Continued*)

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	38.1	78	..	....	..	..	..	....	....	Basal
74.5	37.9	76	21	....	..	..	..	....	....	Fairly quiet
77.4	37.8	74	12	....	..	..	..	.. .	....	Quiet
....	....	..	..	0.78	24	52	24	1.35	45.4	
....	37.8	..	..	....	..	..	..	....	....	Basal
98.7	37.7	82	27	....	..	..	..	....	....	Restless
90.1	37.7	80	27	....	..	..	..	....	....	Restless
....	....	..	..	0.81	19	52	29	1.40	46.1	
....	37.7	..	..	....	..	..	..	....	....	Basal
74.8	37.6	80	13	....	..	..	..	....	....	Very restless
80.9	37.7	..	12	....	..	..	..	....	....	Unsatisfactory because of pain and restlessness
....	....	..	..	0.78	19	59	22	1.49	48.5	
....	37.4	..	..	....	..	..	..	....	....	Basal
67.1	37.3	75	13	....	..	..	..	....	....	Very quiet, turned twice
71.1	37.4	..	8	....	..	..	..	....	....	Very quiet
....	....	..	..	0.81	23	49	28	1.32	43.1	
....	37.6	..	..	....	..	..	..	....	....	Basal
62.4	37.6	76	2	....	..	..	..	....	....	Very quiet
67.8	37.7	..	10	....	..	..	..	....	....	Very quiet until 20 min. before end
....	....	..	..	0.87	22	34	44	1.23	39.2	
....	37.5	..	..	....	..	..	..	.. .	....	Basal
60.3	37.5	64	23	0.82	.	..	.	1.21	40.0	Very quiet

inflammation. The left knee joint was slightly swollen, exquisitely tender and very painful on motion. The left great toe showed marked deformity and moderate tenderness.

Laboratory Examination.—Urine showed a trace of albumin with many granular casts. Phenolsulphonephthalein test: 17 per cent. Blood: leukocytes, 11,000; polymorphonuclears, 66 per cent. Blood uric acid: 7.9 mg. Roentgen-ray examination showed hypertrophic osteoarthritis of all the joints affected.

April 26 he was observed in the calorimeter. His metabolism was found to be 23 per cent. above the average normal. He was restless and suffered much pain. On the following day he had less pain and was quiet. He was again observed and the metabolism was found to be 10 per cent. above the average normal basal. By May 12 he had entirely recovered from the symptoms of his attack. He was again observed in the calorimeter. This time his metabolism was found to be normal. He was discharged May 12, 1917.

The results of the study of basal metabolism will be found in Tables 1 and 4. The first observation on April 26 was unsatisfactory because of the pain and restlessness of the patient. In the two sub-

sequent observations, the metabolism was 12 per cent. and 22 per cent., respectively, above the average normal level, practically within the limits of normal.

TABLE 2.—Clinical Data on John Brown

Date	Body Weight	Estimated Heat Production per 24 Hours	Food			Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	Nitrogen Balance Gm.	24-Hour Urine Volume, C.c.
			Total Calories	Carbohydrate, Gm.	Fat, Gm.					
1/28/17	62.4	.....	1,270	138	52	8.4	23.5	24.3	—15.9	1,670
1/29/17	61.3	2,600	1,320	156	53	7.3	24.4	25.1	—17.8	1,490†
1/30/17	60.5 av.	.....	1,910	156	105	11.3	24.3	25.4	—14.1	1,460
1/31/17	59.7	2,130	2,244	261	109	10.2	21.3	22.3	—12.1	1,220
2/ 1/17	60.0	.....	2,700	243	141	15.4	21.1	22.6	— 7.2	1,510
2/ 2/17	58.5	2,600	2,590	263	128	12.2	20.2	21.4	— 9.2	1,150
2/ 3/17	59.1	.....	3,080	337	141	15.1	21.3	22.8	— 7.7	2,420
2/ 4/17	59.7	.....	3,130	322	153	15.2	20.3	21.8	— 6.6	1,560
2/ 5/17	59.5 av.	.....	3,130	340	144	15.7	20.6	22.2	— 6.5	2,520
2/ 6/17	59.4	.....	3,090	330	146	16.2	19.8	21.4	— 5.2	1,680
2/ 7/17	59.0	.....	3,100	336	144	15.1	20.3	21.8	— 6.7	2,080
2/ 8/17	58.5	.....	2,930	288	147	15.0	18.5	20.0	— 5.0	1,680
2/ 9/17	57.4	2,120	2,880	292	139	15.2	18.7	20.2	— 5.0	1,250
2/10/17	57.6 av.	.....	3,610	381	177	15.6,	18.5	20.1	— 4.5	1,560
2/11/17	57.8	.....	3,500	378	168	15.2	17.7	19.2	— 4.0	1,370
2/12/17	57.7	.....	3,766	428	173	15.3	17.4	18.9	— 3.6	1,790
2/13/17	58.0 av.	.....	3,510	380	160	15.0	15.9	17.4	— 2.4	1,580
2/14/17	58.3	.....	3,730	416	176	15.2	14.6	16.1	— 0.9	1,300
2/15/17	58.3 av.	.....	3,500	378	169	15.1	13.7	15.2	— 0.1	1,960
2/16/17	58.2	.....	3,610	402	169	15.3	14.2	15.7	— 0.4	1,450
2/17/17	58.2 av.	.....	3,500	377	168	15.1	15.0	16.5	— 1.4	1,470
2/18/17	58.3	.....	3,560	389	169	15.5	14.0	15.6	— 0.1	1,100
2/19/17	58.6	.....	3,480	381	165	15.2	14.7	16.2	— 1.0	1,800
2/20/17	59.0	.....	3,470	375	167	15.2	12.6	14.1	+ 1.1	1,300
2/21/17	59.1 av.	.....	3,490	380	165	15.4	12.7	14.2	+ 1.2	1,470
2/22/17	59.3 av.	.....	3,520	368	174	15.3	11.7	13.2	+ 2.1	1,290
2/23/17	59.4 av.	.....	3,520	353	179	15.6	11.5	13.1	+ 2.5	1,360
2/24/17	59.6	.....	3,500	382	167	14.9	11.5	13.0	+ 1.9	1,390
2/25/17	59.6	.....	3,530	388	167	15.1	11.5	13.0	+ 2.1	1,430
2/26/17	59.8	.....	3,560	398	166	15.2	11.9	13.4	+ 1.8	1,530
2/27/17	59.8 av.	.....	3,220	323	162	15.0	11.3	12.8	+ 2.2	1,300
2/28/17	59.9	.....	2,460	308	168	15.2	11.5	13.0	+ 1.5	1,240

* Urine nitrogen plus 10 per cent. food nitrogen.
† About 30 c.c. lost by patient.

METABOLISM IN CHRONIC DEFORMING ARTHRITIS

The basal metabolism of three cases of arthritis deformans was studied. Four cases were examined for evidence of the toxic destruction of protein. The effect of the ingestion of large amounts of protein and carbohydrate was determined in two of the patients. The histories of the four patients follow:

Case 6.—Arthritis Deformans.

History.—Wm. M., a traveling salesman, born in the United States, 50 years of age, was admitted Oct. 16, 1916, and discharged improved Jan. 17, 1917. In 1899 he had gonorrhea followed by epididymitis. The discharge lasted for two weeks. In 1909 he was told that he had syphilis and was treated for a week. As far as he knows, he never had a chancre nor has he shown any secondary symptoms. His wife had three miscarriages at about three months. He has had occasional slight sore throat but no previous attacks of joint pain.

July 21, 1916, he was awakened in the middle of the night by severe pain in the left arm, left wrist and right ankle. He thinks he had some fever. Two days later he went to St. Vincent's Hospital where he was treated until

TABLE 3.—Clinical Data on Arthritis Deformans

Name and Date	Body Wt.	Estimated Heat Production per 24 Hrs.	Food			Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	Nitrogen Balance, Gm.	Urine Volume, C.c.	Length of Period
			Total Calories	Carbohydrate, Gm.	Fat, Gm.						
William B.											
11/21/16	....	.....	2,510	257	115	15.0	14.7	16.2	—1.2	2,300	24 hrs.
11/22/16	65.1	.....	2,610	275	118	15.1	15.7	17.3	—2.2	2,270	24 hrs. 10 min.
11/23/16	65.3	.....	2,470	252	115	14.6	12.7	14.2	+0.4	1,550	23 hrs. 50 min.
11/24/16	65.2	.....	2,520	261	115	14.8	13.4	14.9	+0.1	2,090	24 hrs.
11/25/16	64.7	.....	2,460	250	114	15.1	12.5	14.0	+1.1	1,840	24 hrs.
11/26/16	65.0	.....	2,520	258	115	15.1	13.3	14.8	+0.3	2,080	24 hrs.
11/27/16	....	.....	1,740	164	84	11.2	13.3	14.4	—3.2	2,000	24 hrs.
11/28/16	....	.....	2,530	257	116	14.9	14.7	16.2	—1.3	2,170	24 hrs. 10 min.
11/29/16	64.1	.....	2,530	259	116	15.2	16.1	17.6	—2.4	1,110	23 hrs. 50 min.
11/30/16	64.8	.....	2,240	275†	82†	13.8	14.8	16.2	—2.4	2 030	24 hrs.
12/ 1/16	64.2	.....	2,510	208	114	15.0	11.7	13.2	+1.8	2,180	24 hrs. 5 min.
12/ 2/16	....	.....	2,470	246	115	15.2	12.4	13.9	+1.3	2,070	23 hrs. 55 min.
12/ 3/16	65.4	.....	2,520	258	116	15.2	13.2	14.7	+0.5	2,740	24 hrs.
12/ 4/16	65.3	.....	2,730	310	119	15.9	11.8	13.4	+2.5	2,500	24 hrs.
12/ 5/16	64.6	.....	2,520	266	113	14.6	11.8	13.3	+1.3	1,830	24 hrs.
12/ 6/16	63.7	2,110	2,190	207	108	13.1	11.3	12.6	+0.5	2,020	24 hrs.
12/ 7/16	64.2	.....	2,500	271	106	15.8	12.2	13.9	+1.9	1,890	24 hrs.
12/ 8/16	63.6	2,033	2,000	193	97	13.1	10.6	11.9	+1.2	1,835	24 hrs.
12/ 9/16	64.4	.....	2,600	293	117	15.8	13.2	14.8	+1.0	2,170	24 hrs.
12/10/16	64.8	.....	2,510	261	113	15.1	12.9	14.4	+0.7	2,000	24 hrs.
12/11/16	63.6	1,900	2,350	257	120	15.0	13.2	14.7	+0.3	2,070	24 hrs.
12/12/16	64.6	.....	2,510	260	113	15.2	13.3	14.8	+0.4	1,630	24 hrs.
12/13/16	64.4	2,230	2,300	152	113	24.5	20.7	23.2	+1.3	2,560	24 hrs.
12/14/16	68.6	.....	2,500	296	132	2.4	10.1	10.3	—7.9	1,410	24 hrs.
12/15/16	64.2	.....	2,530	300	132	2.7	6.8	7.1	—4.4	1,200	24 hrs.
12/16/16	65.1	.....	2,520	297	132	2.7	5.7	6.0	—3.3	1,670	24 hrs.
12/17/16	65.2	.....	2,930	346	154	3.4	4.5	4.8	—1.4	1,470	24 hrs.
12/18/16	65.3	.....	2,970	355	154	2.9	3.8	4.1	—1.2	1,220	24 hrs.
12/19/16	66.0	.....	3,020	366	154	3.2	4.0	4.3	—0.3	2,100	24 hrs.
12/20/16	65.9	.....	2,970	355	153	3.4	3.3	3.6	—0.3	1,430	24 hrs.
12/21/16	66.3	.....	2,860	339	150	2.8	3.2	3.5	—0.7	1,700	24 hrs.
12/22/16	66.6	.....	2,830	351	153	2.9	2.9	3.2	—0.3	1,510	24 hrs.
12/23/16	66.5	.....	3,000	369	158	3.2	3.1	3.4	—0.2	1,830	24 hrs.
12/24/16	66.2	.....	2,980	356	154	3.4	3.0	3.3	+0.1	1,700	24 hrs.
12/25/16											
12/26/16	67.0	.....	2,660	295	113	15.2	5.1	6.6	+8.6	2,010	24 hrs.
12/27/16	....	.....	2,530	266	113	15.0	7.1	8.6	+6.4	2,400	24 hrs.
12/28/16	....	.....	3,030	333	136	15.7	7.1	8.7	+7.0	1,320	24 hrs.
12/29/16	65.8	.....	2,800	269	141	15.2	11.2	12.7	+2.5	2,450	24 hrs.
12/30/16	65.7	.....	3,050	328	141	15.1	9.8	11.3	+2.8	1,770	24 hrs.
12/31/16	66.7	.....	3,060	327	142	15.4	12.6	14.1	+1.3	2,280	24 hrs.
1/ 1/17	66.1	.....	3,020	318	143	14.8	11.7	13.2	+1.6	2,210	24 hrs.
1/ 2/17	65.4	.....	3,010	318	142	15.2	11.1	12.6	+2.6	1,950	24 hrs.
1/ 3/17	65.3	.....	3,010	317	142	15.2	8.9	10.4	+4.7	1,40[illegible]	24 hrs.
1/ 4/17	66.5	.....	3,010	317	142	15.0	10.2	11.7	+3.3	1,450	24 hrs.
1/ 5/17	66.3	.....	3,600	318	141	14.9	10.7	12.2	+2.7	1,600	24 hrs.
1/ 6/17	66.5	.....	3,010	319	141	15.1	10.6	13.1	+2.0	1,500	24 hrs.
1/ 7/17	66.4	.....	3,000	336	141	14.7	11.4	12.9	+1.8	2,000	24 hrs.
1/ 8/17	65.8	.....	2,960	318	137	14.9	7.6	9.1	+5.8	1,270	24 hrs.
1/ 9/17	67.1	.....	2,940	315	137	14.6	9.9	11.4	+3.2	1,730	24 hrs.
1/10/17	65.7	.....	1,780	138	102	10.2	8.6	9.6	+0.6	1,976	24 hrs.
1/11/17	65.6	.....	3,020	316	143	15.2	9.7	11.2	+4.0	1,500	24 hrs.
1/12/17	66.8	.....	2,990	318	138	15.4	10.1	11.6	+2.3	1,900	24 hrs.
1/13/17	66.6	.....	3,050	319	145	15.3	11.6	13.1	+2.2	2,310	24 hrs.
1/14/17	66.5	.....	3,010	323	140	14.9	10.6	12.1	+2.8	2,030	24 hrs.
1/15/17	66.2	.....	1,970	207	91	10.2	9.1	10.2	+0.7	2,310	24 hrs.
Edward McK.											
12/21/16	37.5	.....	1,910	181	97	10.2	7.9	8.9	+1.3	815	24 hrs. 40 min.
12/22/16	....	.....	1,350	159	54	7.4	6.8	7.5	—0.1	1,100	24 hrs. 5 min.
12/23/16	....	.....	1,340	152	59	6.5	7.3	8.0	—1.5	1,550	22 hrs.
12/24/16	....	.....	1,220	123	57	7.6	7.4	8.2	—0.6	850	24 hrs. 5 min.
12/25/16											
12/26/16	39.1	.....	1,250	133	56	7.5	7.1	7.9	—0.4	780	24 hrs.
12/27/16	....	.....	1,210	148	57	2.6	4.0‡	....	.....	540	17 hrs.
12/28/16	....	.....	.....	...	...	....	5.1	....	.....	1,020	25 hrs. 40 min.
12/29/16	....	.....	.....	...	...	...	4.5	....	.....	1,550	24 hrs. 10 min.
12/30/16	....	.....	1,500	174	77	2.6	3.6	3.8	—1.2	1,230	
12/31/16-1/1/17	....	.....	1,490	174	77	2.6	3.3	3.6	—1.0	1,080	
1/ 1/17	....	.....	1,490	174	77	2.6	3.1	3.4	—0.8	1,370	
1/ 2/17	....	.....	1,490	174	77	2.6	3.4	3.7	—1.1	890	
1/ 3/17	....	.....	2,050	244	106	2.3	3.4	3.6	—1.3	1,200	24 hrs. 30 m'n.
1/ 4/17	....	.....	2,180	244	121	2.4	3.2	3.4	—1.0	1,500	23 hrs. 45 min
1/ 5/17	38.1	1,533	1,940	241	96	2.2	2.7	2.9	—0.7	1,140	24 hrs. 15 min.
1/ 6/17	....	.....	1,990	235	104	2.4	2.7	2.9	—0.5	1,030	23 hrs. 50 min
1/ 7/17	....	.....	1,880	232	103	2.7	2.6	2.9	—0.2	900	23 hrs. 50 min.
1/ 8/17	38.6	.....	1,530	163	72	7.4	3.3	4.0	+3.4	1,340	24 hrs.
1/ 9/17	....	.....	1,530	161	73	7.5	5.9	6.7	+0.8	1,320	23 hrs. 50 min
1/10/17	....	.....	1,530	160	73	7.6	4.9	5.7	+1.9	1,540	24 hrs.
1/11/17	....	.....	1,500	176	72	7.6	5.1	5.9	+1.7	550	24 hrs.
1/12/17	....	.....	1,520	163	71	7.6	5.5	6.3	+1.3	800	24 hrs.
1/13/17	....	.....	1,550	161	74	7.7	5.9	6.7	+1.0	700	23 hrs. 50 m'n.
1/14/17	....	.....	1,560	162	76	7.4	6.3	7.0	+0.4	830	23 hrs 50 min.
1/15/17	....	.....	.....	...	...	....	5.3	....	.....	1,220	

* Urine nitrogen plus 10 per cent. of food nitrogen.
† Approximate.
‡ Incomplete specimens.

TABLE 3.—Clinical Data on Arthritis Deformans—(*Continued*)

Name and Date	Body Wt.	Estimated Heat Production per 24 Hrs.	Food			Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	Nitrogen Balance, Gm.	Urine Volume, C.c.	Length of Period
			Total Calories	Carbohydrate, Gm.	Fat, Gm.						
Edward R.											
12/21/16	39.5	.....	1,990	196	99	10.6	7.3	8.4	+1.1	450	24 hrs. 15 min.
12/22/16	....	.....	1,340	159	54	7.5	6.6	7.4	+0.1	600	23 hrs. 55 min.
12/23/16	....	.....	1,410	162	58	7.9	5.9	6.7	+1.2	800	24 hrs. 10 min.
12/24/16	....	.....	1,220	123	57	7.6	6.6	7.4	+0.2	1,400	23 hrs. 50 min.
12/25/16											
12/26/16	38.8	.....	1,375	150	56	7.4	5.8	....	.....	420‡	20 hrs. 10 min.
12/27/16	....	.....	1,204	147	57	2.6	3.9	....	.....	940‡	21 hrs. 55 min.
12/28/16	....	.....	1,288	168	57	2.1	3.8	....	.....	1,870‡	22 hrs. 25 min.
12/29/16	....	.....	1,490	174	77	2.6	2.4‡	....	.....	600‡	14 hrs. 45 min.
12/30/16	.. .	.....	1,500	174	77	2.6	4.2‡	....	.....	1,450‡	11 hrs. 20 min.
12/31/16	39.2	.....	1,490	174	77	2.6	3.1	3.4	—0.8	1,800	24 hrs. 35 min.
1/ 1/17	....	.....	1,490	174	77	2.6	3.1	3.4	—0.8	1,610	23 hrs. 50 min.
1/ 2/17	....	.....	1,490	174	77	2.6	3.4	3.7	—1.1	1,750	23 hrs. 40 min.
1/ 3/17	....	1,288	2,000	242	108	2.4	2.3	2.6	—0.2	695	22 hrs. 40 min.
1/ 4/17	....	.....	2,180	244	121	2.4	2.7	2.9	—0.5	1,420	22 hrs. 30 min.
1/ 5/17	....	.....	1,970	231	104	2.3	2 6	2.8	—0.5	1,340	26 hrs. 15 min.
1/ 6/17	....	.....	1,990	235	104	2.3	2.3	2.5	—0.2	1,270	21 hrs. 55 min.
1/ 7/17	37.0	.....	1,770	169	81	12.5	5.3	6 6	+5.9	1,330	23 hrs. 50 min.
1/ 8/17	....	.....	1,450	165	67	7.2	5.4	5.9	—1.3	1,800	26 hrs. 25 min.
1/ 9/17	....	1,764	....	....	....	....	3.4‡	....	.....	1,050‡	17 hrs. 30 min.
1/10/17	....	.....	1,550	161	74	7.8	5.6‡	....	.....	1,810‡	18 hrs.
1/11/17	....	.....	1,660	175	73	8.1	6.0	6.8	+1.3	1,550	24 hrs. 30 min.
1/12/17	....	.....	1,530	163	72	7.5	4.3	5.1	+2.4	1,700	21 hrs. 25 min.
1/13/17	....	.....	1,540	161	73	7.6	5.2	6.0	+1.6	1,250	24 hrs. 10 min.
1/14/17											
1/15/17	....	.....	1,602	170	77	7.4	5.5	6.2	+1.2	1,440	24 hrs.
Frank H.											
11/24/16	40.9	.....	2,520	256	115	14.8	8 9	10.4	+4.4	1,150	24 hrs.
11/25/16	41.1	.....	2,590	277	114	13.3	9.8‡	11.3	+4.0	785‡	24 hrs.
11/26/16	41.1	.....	2,520	260	115	15.1	11.2‡	12.7	+2.4	1,050‡	24 hrs.
11/27/16	41.6	.....	2,470	249	114	15.0	12.6	14.1	+0.9	1,200	24 hrs.
11/28/16	....	.....	2,470	249	112	15.7	12.6	14.2	+1.5	980	24 hrs.
11/29/16	41.5	.....	2,520	250	117	14.6	12.8	14.3	+0.3	960	24 hrs.
11/30/16	41.3	.....	2,160	202	80	13.6	12.8	14.2	—0.6	880	24 hrs.
12/ 1/16	41.5	.....	2,500	255	115	15.6	12.3	13.8	+1.2	900	24 hrs.
12/ 2/16	....	.....	2,450	253	112	15.0	12.1	13.6	+1.5	1,000	24 hrs.
12/ 3/16	42.2	.....	2,490	256	114	14.8	13.4	14.9	—0.1	1,050	24 hrs.
12/ 4/16	42.8	.....	2,530	304	131	2.4	14.5	14.7	—12.3	1,200	24 hrs.
12/ 5/16	41.8	.....	2,580	308	135	2.4	4.7	4.9	—2.5	790	24 hrs.
12/ 6/16	42.3	.....	2,620	290	144	2.1	5.2‡	5.4	—3.3	980‡	24 hrs.
12/ 7/16	41.4	.....	2,530	301	132	2.6	4.0	4.3	—1.7	850	24 hrs.
12/ 8/16	42.0	.....	2,390	298	132	2.4	4.0	4.2	—1.8	780	24 hrs.
12/ 9/16	41.7	.....	2,530	300	132	2.7	4.6	4 9	—2.2	960	24 hrs.
12/10/16	41.6	.....	2,530	301	132	2.6	3.6	3.9	—1.3	1,050	24 hrs.
12/11/16	....	.....	2,540	304	132	2.6	3.5	3.8	—1.2	1,080	24 hrs.
12/12/16	41.4	.....	2,590	317	132	2.7	3.6	3.9	—1.2	930	24 hrs.
12/13/16	....	.....	2,540	304	132	2.6	3.5	3.8	—1.2	1,300	24 hrs.
12/14/16	41.4	.....	2,510	257	132	2.7‡	3.3	3.6	—0.9	675	24 hrs.
12/15/16	41.3	.....	2,480	286	133	2.7‡	4.2	4.5	—1.8	800	24 hrs.
12/16/16	41.1	.....	2,520	298	133	2.6	3.4	3 7	—1.1	600	24 hrs.
12/17/16	42.0	.....	2,290	229	106	14.4	6.5	7.0	+6.5	1,050	24 hrs.
12/18/16	40.7	.....	2,590	298	117	15.7	7.8	9.4	+6.3	1,000	24 hrs.
12/19/16	42.0	.....	2,650	296	113	15.2	8.6	10.1	+5.1	1,100	24 hrs.

* Urine nitrogen plus 10 per cent. of food nitrogen.
‡ Incomplete specimens.

October 16. During this time, his left ankle and right hand were involved. The right ankle improved slightly but the elbows caused great pain. The right elbow gradually stiffened until only slight motion was possible.

Physical Examination.—He was poorly nourished, well developed, rather apathetic man. He had no temperature and was not toxic. The teeth showed moderate pyorrhea. The tonsils were small with rather deep crypts. The right elbow was the site of very painful inflammation. The joint was swollen; the forearm was held at a right angle to the arm. Movement was impossible; the effort was very painful. All of the muscles of the arm and forearm were flabby and wasted. There was but little redness about the swollen parts. The

fingers of the right hand could not be flexed. There was no sign of inflammation, the stiffness probably being due to disuse. There was some limitation of motion, but no pain, in the right shoulder. The left elbow showed thickening of the soft parts but no pain or active inflammation. The right ankle was swollen and slightly painful but not red or hot. The actual involvement of the joint was hidden by a diffuse superficial edema of the foot and ankle. There was slight limitation of dorsal and plantar flexion and some limitation of eversion and inversion. The left ankle was normal. Massage of the prostate caused no discharge. The seminal vesicles were not palpable.

TABLE 4.—SUMMARY OF BASAL METABOLISM STUDIES IN ARTHRITIS

Subject and Diagnosis	Date of Observation	Age, Yrs.	Surface Area, Sq. M.	Average Rectal Temp., C.	Average R. Q.	Average Calories per Hour, Indirect	Per Cent. Deviation from Normal	N* Minimum	Remarks
Edward C. ..... Acute rheumatic fever (mild)	1/22/16	33	1.56	37.3	0.76	64.4	+ 5	.....	Slightly restless
John Br. ..... Gonococcus arthritis	1/29/17	19	1.80	38.4	0.77	94.6	+29	.....	Slightly restless
John Br. ..... Gonococcus arthritis	1/31/17	19	1.78	37.9	0.79	80.8	+11	.....	Quiet
John Br. ..... Gonococcus arthritis	2/ 9/17	19	1.74	37.7	0.81	80.2	+12	.....	Restless
John Bl. ..... Rheumatic fever	1/26/17	58	2.01	37.6	0.76	84.7	+12	.....	Very quiet
Joseph Mc. ..... Gonococcus arthritis	2/ 7/17	27	1.46	37.5	0.82	62.4	+ 8	.....	Very quiet
Timothy S. ..... Gout	4/27/17	42	1.64	37.1	0.82	70.6	+12	.....	Very quiet
Timothy S. ..... Gout	5/12/17	42	1.64	37.6	0.85	64.3	+ 2	.....	Quiet
William B. ..... Severe arthritis deformans	12/11/16	50	1.80	37.0	0.80	72.0	+ 7	2.9-3.3	Quiet
Edward R. ..... Severe arthritis deformans	1/ 3/17	32	1.42	36.9	0.78	48.8	−13	2.6-3.1	Very quiet
Edward McK. ..... Severe arthritis deformans	1/5/17	28	1.37	36.7	0.83	58.1	+ 7	2.6-2.7	Quiet

* Urinary nitrogen for 24 hours on low nitrogen intake.

Laboratory Examination.—Urine: Negative. Blood: Leukocytes, 6,000; polymorphonuclears, 80 per cent.; erythrocytes, 5,000,000; hemoglobin (Sahli) 90 per cent. Nonprotein nitrogen: 57 mg. per 100 c.c. Uric acid: 4 mg. per 100 c.c. Wassermann: negative. Gonococcus fixation test: once positive; twice doubtful.

Roentgen-Ray Reports The teeth showed a considerable amount of alveolar recession, with accentuation of the pericemental membrane, suggesting pyorrhea. There was also an area of rarefaction around the root of the second right upper bicuspid, with imperfect root canal filling. The ankles showed a moderate amount of periarticular atrophy, with a narrowing and clouding of joint spaces,

most marked in the right ankle joint and tarsometatarsal joint, the appearance suggesting an atrophic adhesive osteoarthritis. A similar condition was noticeable in the right elbow.

October 30 the second right bicuspid was extracted. The tooth was dead and somewhat carious in the root canal. On extraction there was a marked putrid pus odor. A culture from the cavity of the gum was negative.

November 27 he had an acute attack of follicular tonsillitis. The temperature rose to 103 F. The right elbow was more swollen and extremely painful. There was pain on any motion of the right shoulder. A tonsil culture showed a pure growth of a nonhemolytic streptococcus. A blood culture was sterile.

December 8, after receiving 200 gm. glucose, he was observed in the calorimeter. On the following day, the joint condition was unchanged. Basal observations were made December 6 and 11. December 13 he was given meat in large quantities and was afterward observed in the calorimeter. From December 19 to January 15 he received frequent doses of Jobling's proteose, the observations on which are mentioned in another article. The joint condition improved very gradually. With constant baking and massage he regained motion in the fingers of the right hand. Motion in the elbow was not increased.

Fig. 4.—William Bl. (Case 6). Roentgenogram of right elbow.

The ankles caused little pain but the edema of the right foot and ankle continued to the time of his discharge on January 17. He was seen again in February. The disease had not advanced. He was working every day but had regained no motion in the elbow.

Case 7.—Arthritis Deformans (many ankyloses).

History.—Edward R., a machinist, born in Austria, 32 years of age, was admitted Dec. 19, 1916, and discharged unimproved Jan. 16, 1917. A sister has deforming arthritis. The patient is a skilled mechanic who had excellent working and home conditions. His habits have been good. He had diphtheria in early childhood. For about one year preceding the onset of the arthritis he expectorated large amounts of foul smelling material which came from the nasal passages and which ceased about the time the joint trouble began. He persistently denies any venereal infection.

In the winter of 1911 he began to have pain in his right great toe. Two weeks later pain appeared in the other toes of the right foot. Soon afterward pain developed in the other foot and before a year had passed both knees were affected. During this time he was able to continue with his occupation but

required help in going to and from work. During the next eight months he was treated in a hospital where traction was applied to his legs. Roentgenograms were taken of his teeth as a result of which one tooth was extracted. While in the hospital the shoulders, elbows, hands, jaws, hips and the sacroiliac synchondroses were involved. In each new joint affected there was some swelling and pain, very severe in the wrists, ankles and toes, moderate in the other joints. The swelling and pain gradually subsided and stiffening occurred. Subsidence was a matter of months or years. So far as he knows, he has never had fever. During the first two years of the illness his weight dropped from 148 to 96 pounds.

Fig. 5.—Edward R. (Case 7). Roentgenogram of left hand.

Physical Examination.—His face was that of a well nourished man. Complexion florid. There was, however, tremendous wasting of the muscles which gave his body the appearance of extreme emaciation. He laid in dorsal decubitus, the thighs in line with the body, the knees extended, the elbows flexed. His skin was moist, shiny and of very fine texture. He was of a cheerful, philosophic disposition. Ears were normal. The teeth and gums appeared healthy. There was no pyorrhea. The tongue and throat could not

be seen because of ankylosis of the jaw. The joints showed many deformities. The jaws could be opened only a quarter of an inch. No lateral motion was possible. There was no tenderness but distinct crepitus over the temporomandibular joints. The right shoulder and wrist, both elbows, hips, knees and ankles were ankylosed but still tender. The sacroiliac joints were tender; very limited motion was possible in the right shoulder. The hands showed extreme deformity which was best demonstrated by the roentgen ray. In both hands were numerous subluxations. There was complete ankylosis of all joints except the distal interphalangeal joints of the right thumb, right fifth finger and left ring finger, which were not at all affected, and the metocarpophalangeal joint of the thumb, which showed free motion but was swollen, very painful and tender. The toes of the left foot were ankylosed. Those of the right foot showed very little motion.

Laboratory Examination.—Urine: Faint trace of albumin; no casts. Blood: Leukocytes, 7,000; polymophonuclears, 60 per cent.; hemoglobin, 85 per cent.; erythrocytes, 5,000,000. Wassermann: strongly positive. Gonococcus fixation test: negative. Nonprotein nitrogen: 45 mg. per 100 c.c. Uric acid: 3 mg. per 100 c.c.

Roentgen-ray report: In the hand there is obliteration of intercarpal, carporadial, metacarpophalangeal and interphalangeal joint spaces with extreme bone atrophy. Examination of hip shows extensive bone atrophy without excrescence formation, also a diminution of the joint space. Knees, shoulders and elbows show a similar condition. There appears to have been in the joints an absorption of the cartilage and a fibrous ankylosis without bone destruction.

While in the hospital he had pain in many of the joints. Pain was most severe and constant in the metacarpophalangeal joints of the thumb which, he says, was the last joint to be affected. About a week after admission he first noted pain and tenderness over the two upper cervical vertebrae which had not been previously involved. At the time of his discharge, January 16, the pain was more severe but no stiffness had developed. His condition was otherwise unchanged.

Case 8.—Arthritis Deformans (many ankyloses).

History.—Edward McK., a machinist, born in the United States, 28 years of age, was admitted Dec. 19, 1916, and discharged unimproved Jan. 16, 1917. In the spring of 1908, while skating, he fell on his right knee. The fall caused him only temporary discomfort. One month later, however, the knee became swollen, stiff and slightly painful. In spite of vigorous treatment during the next two years, the joint did not improve. It was thought at first that it might be tuberculous. In October, 1908, however, a specimen of the joint fluid was injected into a guinea-pig at Roosevelt Hospital with negative results. In 1910, he contracted gonorrhea which lasted three months but did not affect the knee. In 1911, the left knee was involved in a similar manner but with more pain. Four months later the left elbow was affected. During the last year his neck has been stiff and painful and both ankles have been involved. He has received competent local treatments, besides numerous vaccines. All the joints have been affected insidiously. There has never been marked inflammation. So far as the patient knows, he has never had fever.

Physical Examination.—His face was that of a fairly well nourished man. The body and extremities showed marked muscular wasting and moderate emaciation. He was of an unstable, emotional disposition and was overcome by his misfortunes. Two of the molar teeth were carious. There was slight pyorrhea about the incisors. The tonsils were small and red with very deep crypts. The left ear drum showed two large white patches, one posterior, the other anterior to the malleus. There were no signs of active inflammation. The right ear drum was normal. The lungs showed very poor expansion. Massage of the prostate caused no discharge. The shoulders were not affected. The left elbow allowed less than five degrees of motion; it was practically

ankylosed at 100 degrees. The right elbow was ankylosed at 180 degrees. Neither showed signs of active inflammation. The wrists were swollen and tender. The right showed ten degrees of motion; the left even less. The metacarpophalangeal joints of both thumbs and of the right index finger were swollen, tender and painful on motion. The cervical vertebral articulations were completely ankylosed. There was marked tenderness along the cords to the right of the upper three spinous processes. There was slight motion in the vertebral articulations of the dorsal spine and still more in the lumbar region. The hips were completely ankylosed in flexion of 110 degrees to the line of the trunk. The knees were ankylosed, causing the legs to form an angle of 90 degrees with the thighs. The tibia and fibula were subluxated backward and outward on the femur. There was swelling, some tenderness and great pain on

Fig. 6.—Edward McK. (Case 8). Roentgenogram of right knee.

attempted motion in the left ankle which was practically ankylosed. Motion in the right ankle was limited to 30 degrees.

Laboratory Examination.—Urine: Negative. Blood: Leukocytes, 12,500; polymorphonuclears, 75 per cent.; erythrocytes, 4,700,000; hemoglobin, 90 per cent. Gonococcus fixation test: doubtful. Cultures from both tonsils showed an almost pure growth of *Staphylococcus aureus* with a few colonies of *Streptococcus viridans.* Nonprotein nitrogen: 24 mg. per 100 c.c. Uric acid: too low to estimate.

Roentgen-ray Report: Examination showed osteoarthritis deformans with excrescence formation. There was marked subluxation at the knee joint. The elbows and tarsal joints showed evidence of atrophy, diminution in the size of the joint space, but no bone destruction.

January 11 he developed herpes zoster along the course of the fourth and fifth intercostal nerves. Vesicles were numerous but pain was very slight. January 16 he was transferred to the Metropolitan Hospital unimproved.

CASE 9.—Arthritis Deformans; scabies.

History.—Frank H., a proof-reader, born in the United States, 61 years of age, was admitted Nov. 4, 1916, and discharged unimproved Dec. 20, 1916. His wife died of "rheumatic gout" at the age of 41. He has led a sedentary life, is very moderate user of alcohol and tobacco. He has had gonorrhea five or six times, the last attack ten years ago. History of "hard chancre" twenty-five years ago; two soft chancres since then. No history of secondary syphilis,

Fig. 7.—Frank H. (Case 9). Roentgenogram of right knee.

or of any specific treatment. He has never had tonsillitis or alveolar abscesses. He has not suffered from respiratory infections. No history of rheumatic fever or heart disease.

About seven years ago he developed a stiffness in the right knee which gradually became worse. Five years ago, the left knee began to get stiff. For the past two years he has noticed a gradually increasing stiffness and outward deflection of the fingers of both hands. The right knee has been painful at times, but there has never been much pain in the fingers, even on flexion. Recently there has been stiffness in both shoulders and in the spine. Patient thinks he had some urethral discharge at the beginning of his illness. He has lost some weight, but does not know how much.

Physical Examination.—Patient was a middle-aged man, poorly nourished and somewhat under-developed. Teeth: All molars missing, except two on

lower left side which were markedly carious; considerable pyorrhea present, particularly of lower incisors which were loose in sockets; no tenderness of gums. Throat: Tonsils red but not enlarged. Several posterior lymph nodes enlarged on both sides. Heart: Measured 8 cm. to left in fifth space; apex impulse not felt; right border of heart at right sternal margin; sounds faintly heard, faint systolic murmur at apex heard also over sternum; action slow and regular. Over the entire body, more marked on abdomen and arms, there were numerous small petechiae, apparently the result of scratching; also many small ecchymoses and scabs. Tendon reflexes all exaggerated. Joints: Spine straight. Considerable limitation of movement, especially in dorsal region when patient bends forward. Flexion was from the hips, the spine remaining rigid. Lateral motion was from the lumbar region. Shoulder joints: Arms could be elevated to an angle of only 45 degrees. Motion in shoulder joints considerably limited, especially in abduction and rotation. Flexion and extension good. Wrist joints showed some limitation of flexion and extension. There was moderate atrophy of infraspinatus and supraspinatus muscles. Metacarpals, phalanges and knuckles very prominent on both hands due, in part, to atrophy of the interossei muscles. There was considerable limitation of extension of all fingers on both hands (45 degrees). Flexion of fingers not limited. Moderate contraction of flexor tendons, more marked on left side. Hips: Limitation of abduction (30 degrees). Patient stood with legs bowed, knees prominent on account of a marked atrophy of the muscles, more marked on the left side. Right knee measured 33 cm., left the same. Flexion of knee joints, 90 degrees. No fluid in knee joints, ankles normal. Toe joints normal.

Laboratory Examination.—Urine: very faint trace of albumin; no casts. Phenolsulphonephthalein test: first hour, 42 per cent., second hour, 23 per cent. Sputum: Many streptococci: no tubercle bacilli.

Roentgen ray Report: In the chest the aortic shadow was somewhat broader than normal; otherwise, the findings were negative. The hands showed periarticular atrophy of the bones with narrowing of the joint spaces, and rarefaction of the articular borders. Roentgenogram of the right femur showed cortical thickening of the femur with bowing and rarefaction. The skull showed a similar rarefaction. The findings were those of an atrophic osteo-arthritis.

During the patient's stay in the hospital he suffered from a subacute bronchitis which at one time showed an acute exacerbation. The condition in his joints remained practically unchanged.

The four cases of arthritis deformans were all of severe type, of long duration, showing great deformities; in fact, two of the patients (Cases 6 and 7) were so crippled that it was difficult to collect twenty-four hour specimens of urine and almost impossible to make them end the period exactly on the minute according to the custom of the metabolism ward. Since each voiding was collected in a separate bottle, and the time of voiding recorded at once, it did not destroy the value of the observation if the urine secreted during one or two hours was lost. The last columns in Table 3 (Clinical data) show the exact time of all complete and incomplete specimens. The results of observations on the basal metabolism of these patients will be found in Tables 1 and 4. The effects of large carbohydrate and protein meals are represented in Figures 8 and 9.

DISCUSSION OF CHRONIC DEFORMING ARTHRITIS

By a majority of writers, chronic deforming arthritis has been considered a manifestation of infection from some septic focus within the body. By others, it is thought to be a disease of metabolism. In considering the results obtained from the study of these few cases, the two prevailing conceptions of etiology should be kept in mind.

The wasting and emaciation which accompany long standing infection have led often to the assumption that in such diseases there is an increase in basal metabolism and a toxic destruction of body protein. This assumption has never been properly confirmed. In the chronic infection of tuberculosis, several cases of which have been studied by McCann and Barr,[8] only slight toxic destruction of protein was found. The level of metabolism was in certain cases increased but the increase was usually accompanied by a considerable elevation of body temperature. Our knowledge of these factors in other chronic infections is fragmentary and incomplete. If one thinks of deforming arthritis as a chronic infection, facts concerning the level of basal metabolism and possible destruction of body protein are of considerable importance.

Basal Metabolism.—By referring to Table 6, it will be seen that two of the patients gave basal figures 7 per cent. above the average, in other words, within the limits of normal. One gave results 13 per cent. below the average but he was emaciated to nothing but skin, bones and ankylosed joints. One usually finds a low metabolism in such profound undernutrition. There is a most satisfactory agreement between the methods of direct and indirect calorimetry. The total in all experiments by the direct method was 1381.5 calories, by the indirect method 1376.5 calories, a difference of 0.3 per cent. The respiratory quotients were at all times normal and indicated no disturbance in the proportion of calories obtained from the different food constituents. In the study of these three cases, no disturbance of the normal basal metabolism has been detected.

Nitrogen Balance.—By referring to Table 3, it will be observed that nitrogenous equilibrium was maintained in all four cases, except when the nitrogen intake was cut to a very low figure. Even then the nitrogen excreted never exceeded the food nitrogen by more than a few grams. Furthermore, by reducing the nitrogen intake to a minimum it was possible to reduce the nitrogen excretion of these patients to as low a level as is possible with normal, healthy individuals. For instance, William B. for five consecutive days excreted less than 3.6 gm. nitrogen per day; Edward McK., less than 2.7 gm. for three days; Frank H., less than 3.6 gm. for five days. Edward R.

8. McCann, W. S., and Barr, D. P.: Clinical Calorimetry. Paper 29. The Metabolism in Tuberculosis. Arch. Int. Med. **26**:663 (Nov.) 1920.

averaged about 3 gm. for a considerable period, but his figures are somewhat uncertain since he lost a few specimens, as is indicated in the last column of this table. All of these results are within the normal limits found by Landergren, Kocher and others, and they indicate that there is no toxic destruction of protein in chronic arthritis.

If chronic deforming arthritis is a disease of metabolism, one may expect to find some evidence of diminished ability to metabolize one or more of the food stuffs. Pemberton's extensive studies have demonstrated practically nothing abnormal except a high glucose content of the blood following glucose ingestion. It must be said, that high sugar curves are also found in diabetes, hyperthyroidism, nephritis, severe infections and various other conditions. Even in supposedly normal individuals the curve of sugar in the blood after ingestion of glucose varies so much that conclusions drawn from apparently abnormal figures may be very misleading.

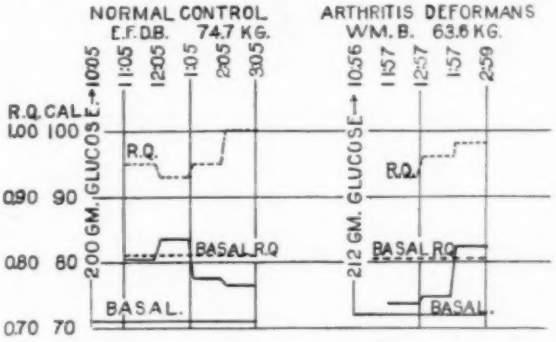

Fig. 8—Comparison of normal control and arthritis patient in their response to large carbohydrate meal. Solid lines—level of metabolism; dotted line, respiratory quotient.

Perhaps, a more direct way of securing evidence of the body's ability to handle food stuffs is by a study of the respiratory quotients and the specific dynamic action of the different classes of food following their ingestion. Experiments of this kind were done in two of the cases of chronic arthritis. December 8, William Bl. received 212 gm. dextrose one hour before going into the calorimeter. He remained in the calorimeter three hours. December 13, the same patient received 662 gm. chopped meat (24.3 gm. nitrogen) before going into the calorimeter. January 9, Edward R. was given 212 gm. glucose and was studied in the calorimeter. In Figures 8 and 9 the curves for heat production as determined by the indirect method and the respiratory quotients are compared with normal controls studied in Paper IV

of this series. The results are in no way conclusive, but there are no significant differences which would indicate an inability to oxidize either protein or carbohydrate.

The observations give no indication that arthritis deformans is a disease of metabolism. The patients studied were of the type usually considered to be the result of a chronic infective process. If this be

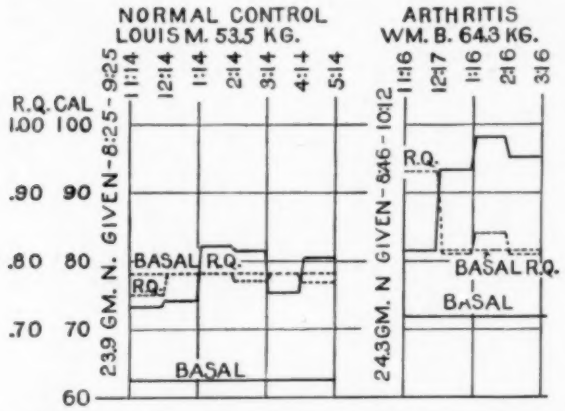

Fig. 9.—Comparison of normal control and arthritis patient in their response to a large protein meal. Solid lines—level of metabolism, dotted line, respiratory quotient.

the correct conception, one may say that the infection was unaccompanied by changes in the level of basal metabolism or by toxic destruction of protein.

SUMMARY AND CONCLUSIONS

1. Three cases of acute and subacute arthritis showed no variation from the normal basal metabolism. One case of acute arthritis observed during a continuous temperature of 38.4 C. showed a basal metabolism 26 per cent. above the average normal level. Other observations on the same patient during afebrile periods exhibited a metabolism practically within normal limits. In this case there was a marked loss of body nitrogen during a period when the energy requirement was more than covered by a liberal diet. This indicates a toxic destruction of body protein.

2. One case of gout showed little change in the level of basal metabolism.

3. Four cases of severe arthritis deformans on the Landergren diet, very low in protein but high in calories, excreted from 2.6 to 3.6 gm. nitrogen per day, figures which are well within the normal limits.

Three of these patients when tested in the calorimeter had a metabolism rate close to the average normal level. The respiratory quotients were normal, and there was no evidence of abnormal respiratory metabolism following the ingestion of large test meals of glucose and protein.

4. The observations on arthritis deformans do not indicate that it is a disease of metabolism. If infectious in origin, it may be said that the infection is not accompanied by increase in basal metabolism or by toxic destruction of body protein.

CLINICAL CALORIMETRY XXXII

TEMPERATURE REGULATION AFTER THE INTRAVENOUS INJECTION OF PROTEOSE AND TYPHOID VACCINE *

DAVID P. BARR, M.D., RUSSELL L. CECIL, M.D.
AND EUGENE F. DU BOIS, M.D.
WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM
NEW YORK

During the last seven or eight years, many clinicians have been treating arthritic patients by means of intravenous injections of foreign protein. These produce chills which resemble malarial paroxysms and afford an ideal opportunity for studying in man the phenomena of temperature regulation. In 1917 the chills and fever in several cases of malaria were studied in the Sage calorimeter.[1] The present investigation was undertaken as a supplement to the work in malaria in order to study in more detail the mechanism of the rise and fall of body temperature.

The gaseous exchanges of patients have been studied by Kraus and Chvostek [2] after giving tuberculin, and in animals by Freund and Grafe,[3] Versar, who gave infusions of sodium chlorid,[4] and by Berrar,[5] who used aloin. In general, these animal experiments showed a rise in total oxidative processes accompanying the rise in temperature. Sometimes this increase amounted to 130 per cent.

The other phenomena which follow the intravenous injection of foreign protein have been studied in many clinics since the therapeutic application of this procedure was developed by Ichikawa, Kraus, Jobling and Petersen and others. Miller and Lusk [6] reported favorable results in arthritis and many others have tried their methods and have

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Paper 28, The Metabolism in Malarial Fever, Arch. Int. Med. **21**:627 (May) 1918.

2. Kraus, Fr., and Chvostek, F.: Ueber den respiratorischen Gaswechsel im Fieberanfall nach Injection der Koch'schen Flüssigkeit, Wien. klin. Wchnschr. **4**:104, 1891.

3. Freund, H., & Schlagentweit, E.: Ueber die Waerme Regulation Kurarisierter Tiere, Arch. f. Exper. Path. u. Pharmakol. **69**:12, 1912.

4. Verzar, Fritz.: Die Wirkung intravenöser Kochsalzinfusionen auf den respiratorischen Gaswechsel, Biochem. Ztschr. **34**:41, 1911.

5. Berrar, M.: Die Wirkung des Aloins auf den Stoffwechsel, Biochem. Ztschr. **49**:426, 1913.

6. Miller, J. L., and Lusk, F. B.: The Treatment of Arthritis by Intravenous Injection of Foreign Protein, J. A. M. A. **66**:1756 (June 3) 1916; The Use of Foreign Protein in the Treatment of Arthritis, J. A. M. A. **67**:2010 (Dec. 30) 1916.

investigated the physiologic changes which accompany the paroxysm. Cecil [7] has made a clinical study of forty cases treated in this hospital, including in his series the cases published in this article. He obtained fairly satisfactory results but did not consider that treatment with foreign proteins was indicated until salicylates had been given a thorough trial. Snyder [8] used the same New York City Board of Health typhoid vaccine, starting with small doses.

Scully [9] made a careful study of the blood count, temperature and blood pressure after intravenous injections and published composite curves which are most instructive. He used typhoid vaccine in doses of from 37 to 75 million bacilli with patients suffering from acute articular rheumatism. The composite temperature curve reached a maximum of 103.6 F. four hours after the injection and fell gradually to normal in sixteen hours. The highest individual temperature was 106.6 F.; the lowest 102 F. The leukocytes showed first a fall and then a sharp rise. The average count was 14,000 at the time of injection. During the chill it dropped to 5,000 but rose to 40,000 about eight hours after the vaccine was given. The highest individual count was 77,200 at six hours; the lowest 13,600. The blood pressure probably rose during the chill but accurate measurements were impossible. After the chill, the composite curve showed a fall, reaching 92 mm. systolic and 60 mm. diastolic pressure six hours after the injection. Following this there was a gradual rise. The lowest individual reading was 60 mm. systolic and 40 mm. diastolic, the patient evidently suffering from marked shock. In addition to these phenomena, Scully examined the urine but found no marked changes.

Cowie and Calhoun [10] have emphasized the analogy between the nonspecific chill and the malarial paroxysm. They made numerous blood counts and found nucleated red cells and myelocytes and many atypical cell forms, particularly in the lymphocyte group. Jobling, Petersen and their co-workers [11] have studied in detail the ferments after the injection of foreign protein. They have found an instantaneous mobilization of a large amount of nonspecific proteose; decrease in antiferment; increase in noncoagulable nitrogen of the serum; increase in amino-acids; and a primary decrease in serum

7. Cecil, R. L.: A Report on Forty Cases of Acute Arthritis Treated by Intravenous Injections of Foreign Protein, Arch. Int. Med. **20**:951 (Dec.) 1917.

8. Snyder, R. G.: A Clinical Report of Nonspecific Protein Therapy in the Treatment of Arthritis, Arch. Int. Med. **22**:224 (Aug.) 1918.

9. Scully, F. J.: The Reaction after Intravenous Injections of Foreign Proteins, J. A. M. A. **69**:20 (July 7) 1917.

10. Cowie, D. M., and Calhoun, H.: Nonspecific Therapy in Arthritis and Infections, Arch. Int. Med. **29**:69 (Jan.) 1919.

11. Jobling, J. W.: Petersen, W., and Eggstein, A. A.: Studies on Ferment Action, J. Exper. M. **22**:401, 568, etc., 1915; Petersen, Wm. H.: Serum Changes Following Protein "Shock" Therapy, Arch. Int. Med. **20**:716 (Nov.) 1917.

proteoses. There is also an increased flow of lymph from the thoracic duct. Later there is a progressive increase in the noncoagulable nitrogen, in proteoses and serum lipase.

We must remember that while all these changes are taking place in the blood and cardiovascular system, the organism is being subjected to great variations in the degree of muscular activity, marked fluctuations in the respiratory activity, sudden demands for the mobilization of foodstuffs with increased products of katabolism, and also rapid changes in the temperature of the body cells. These metabolic and physical phenomena form the subject of the present investigation.

The apparatus used was the respiration calorimeter described in the previous papers of this series and the patients were kept under close observation in the metabolism ward. On account of the length of the observations, it was necessary to allow them some food shortly before the start of the experiment. All, with the exception of Albert G., were given a small "standard breakfast" four or five hours before the start of the observation. It has been shown in Paper 26 [12] of this series that this breakfast has no effect on the metabolism, except for two or three hours after it has been taken.

The subjects were five patients with various rheumatic affections, one comparatively well man with lumbar and sciatic pains and one normal control. Three of the patients were studied from the standpoint of possible changes in metabolism which might occur in chronic arthritis. The results of observations on their basal metabolism may be found in the accompanying article on arthritis. At the time of the observations there were in the general wards of the hospital a considerable number of patients being treated with intravenous injections of protein made according to the method of Jobling or with typhoid vaccine as prepared by the New York City Board of Health. The other two rheumatic subjects were intelligent men selected from among these patients. Both had previously given definite response to injections of foreign protein. In these, it seemed possible to calculate fairly closely the time interval between a given dose and the onset of a chill. This was a matter of importance since the technic of managing a calorimeter in short periods during a chill is extremely difficult. With one subject (Genaro A.), a rise in temperature followed the injection but the chill did not occur. Albert G., the normal control, and R. L. C., had never been given foreign protein before; yet, neither had the expected chill. All of the others reacted very much in the manner predicted.

12. Soderstrom, G. F.; Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Paper 26, The Effect of a Small Breakfast on Heat Production, Arch. Int. Med. **21**:613 (May) 1918.

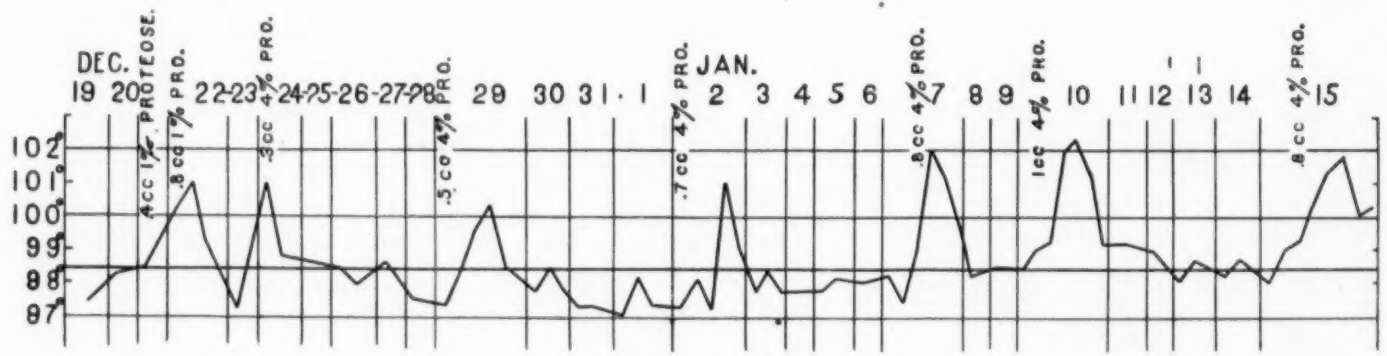

Fig. 1—Temperature curve of William B.

TABLE 1.—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
R. L. C.*	Prelim.	11:48	....	....	....	....	....	....	....
1/19/17, 62.3 Kg. (Ht.-Wt.) 1.77 Sq. M.	1	1:48	46.4	43.1	0.78	57.9	0.49	142.3	....
William B.	Prelim.	11:40	....	....	....	....	....	....	....
1/15/17 66.2 Kg. 1:80 Sq. M.	1	12:20	24.1	20.2	0.87	22.3	0.43	68.6	50.1
	2	12:50	39.0	32.6	0.87	26.4	0.43	111.2	40.4
	3	1:50	24.3	28.4	0.62	40.0	0.43	92.8‡	88.9
	4	2:50	28.6	26.8	0.78	39.5	0.43	88.8	92.5
Albert G.	Prelim.	1:07	....	....	....	....	....	....	....
1/13/15 66.8 Kg. 2.07 Sq. M. Meeh Formula	1	2:07	22.5	19.0	0.86	28.0	0.48	64.0	69.0
	2	3:07	26.7	21.2	0.92	29.7	0.42	72.5	74.1
	3	4:07	25.2	23.8	0.77	30.2	0.42	78.6	78.8
	4	5:07	25.0	22.7	0.80	31.2	0.42	75.4	73.2
John Br.	Prelim.	11:19	....	....	....	....	....	....	....
2/2/17 58.5 Kg. 1.75 Sq. M. (Ht.-Wt.)	1	12:19	54.8	44.7	0.89	29.0	0.68	152.8	70.6
	2	12:49	16.8	14.3	0.86	15.9	0.68	48.5	42.2
	3	1:19	15.6	13.8	0.82	15.6	0.68	46.4	44.1
	4	2:19	31.7	31.0	0.74	32.1	0.68	102.1	93.5
	5	3:19	31.4	28.8	0.79	46.9	0.68	98.1	112.2
Joseph McC.	Prelim.	11:09	....	....	....	....	....	....	....
2/7/17 51.4 Kg. 1.40 Sq. M.	1	12:00	20.9	18.6	0.82	27.8	0.27	62.4	61.5
	2	12:46	....	....	....	....	0.27	....	....
	3	1:15	8.6	10.1	0.79	13.4	0.27	58.2	27.8
	4	1:41	10.4	7.4		13.8	0.27		28.6
	5	2:41	29.6	27.0	0.80	32.6	0.27	90.3	66.1
	6	3:41	22.7	21.9	0.76	30.6	0.27	72.1	66.4
	Aver.	.....	....	....	....	....	....	....	....
Joseph McC.	Prelim.	9:28	....	....	....	....	....	....	....
2/12-13/17 51.6 Kg. 1.46 Sq. M.	1	9:58	10.7	8.0	0.87	9.8	0.16	30.3	26.3
	2	10:30	7.8	6.2	0.91	7.7	0.16	21.1	20.6
	3	11:00	28.1	22.4	0.92	17.6	0.16	77.1	44.6
	4	12:00	23.3	20.7	0.82	24.5	0.16	69.7	62.8
	5	1:00	27.1	23.4	0.84	27.2	0.16	79.3	68.7
	6	1:40	....	....	....	....	....	....	....
	7	2:40	22.4	19.7	0.83	26.3	0.16	66.5	69.3
	8	3:40	21.3	19.0	0.82	29.8	0.16	62.7	75.3
	9	4:40	20.7	18.2	0.83	26.7	0.16	61.3	68.8
	10	5:30	18.8	17.0	0.81	23.9	0.16	56.7	63.6
	11	6:00	10.7	9.1	0.85	12.9	0.16	30.8	34.0

* Direct lost because of leak in pipes of ice tank.
† Spirometer string broke in first and third periods.
‡ Calculated from R. Q. of 0.70.

—Calorimeter Data

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
...	35.6	..	..	....	..	..	..	....	....	Proteose 4% (Jobling) 0.5 c.c. at 10:05 a. m.
...	36.9	..	32	0.78	18	62	20	1.13	40.2	Quiet, no chill
....	37.3	..	..	....	..	..	..	....	....	Proteose 4% (Jobling) 0.8 c.c. at 9:18 a. m.
67.4	37.6	60	34	0.88	11	37	52	1.55	57.2	Shivering last 5 min.
104.0	38.6	..	21	0.87	20	26	54	3.36	123.5	Chill 12:20-12:40
115.4	39.1	79	14	0.60	..	..	..	1.40	....	Fairly quiet
62.6	38.6	76	14	0.77	13	48	39	1.34	49.3	Quiet
....	36.8	..	..	....	..	..	..	....	....	Typhoid vaccine 500 million subcutaneously 10:07 a. m.
64.2	36.7	65	13	0.90	30	27	53	0.96	Meeh 30.9	Quiet
90.5	37.0	60	28	0.94	15	17	68	1.09	35.0	Quiet
77.3	37.0	60	24	0.76	14	70	16	1.18	37 9	Rather restless
74.4	37.0	..	28	0.80	15	58	27	1.13	36 4	Rahter restless
....	37.8	..	..	....	..	..	..	....	....	Typhoid vaccine 25 million intravenously at 10:50 a. m.
120.6	39.2	..	25	0.90	10	30	60	3.14	105.0	Chill, 30 min.
76.1	39.9	..	10	0.87	19	35	46	1.64	54.8	Quiet, voided
38.2	39.8	..	7	0.82	20	48	32	1.56	52.6	Quiet
87.5	39.7	..	20	0.73	18	76	6	1.73	57.7	Quiet
86.9	39.2	98	32	0.79	19	60	21	1.63	54.5	Somewhat restless
....	37.5	..	..	....	..	..	..	....	....	Basal
60.3	37.5	64	23	0.82	..	..	..	1.21	42.7	Very quiet
....	37.5	..	..	....	..	..	..	....	....	Removed from calorimeter, typhoid vaccine 40 million intravenously at 12:31 p. m.
20.4	37.3	58	12	0.79	..	..	..	1.24	40.7	Quiet
29.4	37.3	56	8							
112 0	38.4	..	12	0.79	..	..	..	1.76	57.9	Chill, 1:45-2:15 p. m.
79.0	38.8	..	..	0.75	..	..	..	1.40	46.2	Very quiet
....	....	..	..	....	10	65	25			
....	37.2	..	..	....	..	..	..	....	....	Typhoid vaccine 50 million intravenously at 9:05 p. m.
18 0	37.1	72	8	0 88	7	37	56	1.18	41.5	Quiet
20.5	37.1	..	2	0.90	8	30	62	1.11	39.5	Very quiet
92.8	38.2	80	7	0.92	4	26	70	2.24	79 3	Chill, 10:21-10:53 p. m.
70.2	38.4	120	..	0.82	6	58	36	1.35	47.7	Quiet
78.3	38.3	..	20	0.84	5	52	43	1.53	54 3	Fairly quiet
....	38.5	..	..	....	..	..	..	....	....	Removed from calorimeter, given 240 c.c. water at 1:05 (37°)
57.4	38.2	70	9	0.83	6	56	38	1.29	45.5	Very quiet
62.2	37.9	..	7	0.82	7	57	36	1.23	43.6	Asleep
62.0	37.8	88	4	0.83	7	53	40	1.19	42 0	Very quiet
59.9	37.7	..	13	0.81	6	62	32	1.32	46.4	Very quiet
30.9	37.6	..	8	0 86	7	51	42	1.20	42 2	Restless last 5 min.

TABLE 1.—CALORIMETER—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Frank G.†..... 2/23/17 56.7 Kg. 1.56 Sq. M.	Prelim.	11:15	....	....	....	....	....	....	....
	1	11:45	11.0	9.9†	0.81	20.7	0.29	32.2	32.8
	2	12:45	40.9	35.6	0.84	37.7	0.29	130.1	68.6
	3	1:45	26.0	23.1†	0.82	38.5	0.29	77.4	74.0
	4	2:45	25.2	24.4	0.75	51.0	0.29	80.3	90.6
	5	3:53	24.1	27.5	0.64	73.8	0.29	89.7	110.1
Genaro A..... 3/2/17 52.9 Kg. 1.56 Sq. M.	Prelim.	11:15	....	....	....	....	....	....	....
	1	11:45	12.1	9.9	0.89	12.9	0.68	33.3	32.1
	2	12:15	13.2	11.9	0.80	15.6	0.68	39.4	37.7
	3	1:15	25.9	23.5	0.80	32.3	0.68	77.7	68.7
	4	2:15	26.2	25.0	0.76	33.8	0.68	82.0	71.1
	5	3:15	27.2	26.2	0.76	36.5	0.68	85.8	78.7

* Direct lost because of leak in pipes of ice tank.
† Spirometer string broke in first and third periods.
‡ Calculated from R. Q. of 0.70.

CASE HISTORIES

CASE 1.—R. L. C., a physician, born in the United States, 35 years of age, has never been seriously ill, has had no attacks of tonsillitis or of articular rheumatism. During the winter of the past three or four years he has had lumbar and sciatic pains, which, at times, have entirely incapacitated him. At the time of the observation he was in the midst of a particularly uncomfortable attack.

Physical Examination.—Nothing abnormal. Tonsils are small and healthy in appearance. The teeth are in good condition. No areas of tenderness are found in the back or in the region of the sciatic nerve.

Jan. 19, 1917, he was given intravenously 0.5 c.c. of a 4 per cent. solution of Jobling's proteose. No rise in temperature or disagreeable symptoms followed the injection. No improvement of pain or stiffness resulted.

The calorimeter observation was unsatisfactory because there was no chill. A leak in the pipe made it impossible to use the method of direct calorimetry in this experiment.

CASE 2.—William B., arthritis deformans (gonorrheal?), a traveling salesman, born in the United States, 50 years of age, was admitted Oct. 16, 1916, and discharged improved Jan. 17, 1917. In 1899 he had gonorrhea followed by epididymitis. The discharge lasted for two weeks. He had had occasional sore throat but no previous attacks of joint pain.

July 21, 1916, he was seized with pain in the left arm and wrist and in the right ankle. Two days later he went to St. Vincent's Hospital where he was treated until Oct. 16.

Physical Examination.—He is a poorly nourished, well developed rather apathetic man. He has no temperature and is not toxic. The right elbow is ankylosed and is very painful. All of the muscles of the right arm and forearm are flabby and wasted. The fingers of the right hand are stiff from disuse. The right shoulder, left elbow and right ankle are very moderately involved. There is superficial edema of the feet and ankles.

—DATA—(*Continued*)

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	37.5	..	..	....	..	..	..	....	....	Typhoid vaccine 35 million intravenously at 10:51 a. m.
29.8	37.4	84	7	0.81	10	58	32	1.18	42.6	Quiet, asleep
120.7	39.1	96	..	0.84	6	51	43	2.12	77.0	Chill, 11:58 a. m. - 12:25 p. m.; drank 240 c.c. water (37 C.) 12:37 p.m.
76.5	39.2	90	10	0.82	10	54	36	1.37	49.6	Restless for 50 min.
73.2	38.9	..	6	0.75	10	77	13	1.42	51.5	Restless last 10 min.
93.0	38.6	..	18	0.62	..	..	..	1.58	57.5	
....	37.6	..	..	....	..	..	..	....	....	Typhoid vaccine 30 million intravenously at 10:50 a. m.
33.0	37.6	66	1	0.92	27	20	53	1.26	42.7	Very quiet
40.4	37.7	..	5	0.80	23	44	33	1.50	50.5	Almost motionless
85.0	38.1	..	3	0.80	23	52	25	1.47	49.8	Almost motionless
80.5	38.3	74	3	0.75	22	68	10	1.55	52.6	Almost motionless
76.5	38.3	..	2	0.74	21	70	9	1.62	55.0	Almost motionless

November 27 he had an acute attack of follicular tonsillitis from which he recovered rapidly. From December 19 to January 15 he received at rather irregular intervals eight doses of Jobling's proteose intravenously. From the first dose he had no reaction. Both the first and second injections were of a 1 per cent. solution; the others were of a 4 per cent. solution, varying in dose from 0.3 c.c. to 1.0 c.c.

January 10 and January 15 he was observed in the calorimeter following proteose injections. Owing to technical errors, the observation of January 10 was lost. That taken on the fifteenth is here presented. No marked change in symptoms was noted after any of the proteose injections. The joint condition improved very gradually. With constant baking and massage he regained motion in the fingers of the right hand. The elbow was still ankylosed at the time of discharge, January 17.

CASE 3.—Albert G., a normal control to whom typhoid vaccine was given subcutaneously, a laborer born in Italy, 24 years of age, was admitted Dec. 14, 1914, and discharged Jan. 14, 1915. His health was excellent. He was out of work and was admitted to the hospital to act as a normal control for other observations which were being carried on at the time. He was short, with large muscles and very little subcutaneous fat. He was neurasthenic, continually fearing that he would become ill.

January 13, at 10:07 a. m., he was given 500 million dead typhoid bacilli (New York City Board of Health vaccine) subcutaneously into the arm. The usual reaction occurred with moderate swelling and tenderness of the arm.[13]

CASE 4.—John Br., acute arthritis, gonorrheal (rheumatic?), a clerk born in the United States, 19 years of age, was admitted Jan. 25, 1917, and discharged

13. For details of previous observations on this man, consult Soderstrom, G. F.; Meyer, A. L., and Du Bois, E. F.: Clinical Calorimetry, Paper 11, A Comparison of the Metabolism of Men Flat in Bed and Sitting in a Steamer Chair, Arch. Int. Med. **17**:872 (July) 1916; Gephart, F. C., and Du Bois, E. F.: Clinical Calorimetry, Paper 13, The Basal Metabolism of Normal Adults with Special Reference to Surface Area, Arch. Int. Med. **17**:902 (June) 1916.

improved March 23, 1917. January 7 he began to have a urethral discharge. Six days later he was seized with pain in the right knee, right foot, left foot and right thumb.

Physical Examination.—Patient was a well developed, somewhat emaciated boy, acutely ill, rather toxic. The tongue was slightly dry, with a brown coat. The left knee joint is distended with fluid, hot, slightly tender and held in semiflexion. The right knee, both ankles and some of the small joints of the hands and feet show swelling and moderate tenderness. There is a urethral discharge containing gonococci in large numbers.

January 29 and January 31 he was observed in the calorimeter. February 2 he was given intravenously a 25 million dose of New York City Board of Health typhoid vaccine and was observed in the calorimeter. On the fourth and again on the fourteenth he received typhoid vaccine. On March 1 he was discharged to the general ward, very slightly improved by the vaccine therapy. He was later given gonococcus vaccine intravenously. Following this his improvement was rapid. He was discharged from the hospital March 23 with slight swelling in his right knee joint but with no other symptoms.

Case 5.—Joseph McC., subacute gonorrheal arthritis, an elevator operator, born in the United States, 27 years of age, was admitted Jan. 24, 1917, and discharged unimproved. In 1910 he had an attack of gonorrheal urethritis followed by epididymitis. Since then he has had a urethral discharge several times, the last time being in November, 1916. In 1912 he had an acute arthritis involving all the joints and he was ill for nine weeks. A second attack of the same character, in 1914, lasted two months. He has never had sore throat, chorea or other manifestations of acute rheumatic fever.

Jan. 3, 1917, he began to have a dull pain in the lower end of the spine and in the lumbosacral muscles which radiated down the right thigh. His right heel became so painful that he could not walk. About the same time the urethral discharge recommenced.

Physical Examination.—This shows an under developed, poorly nourished man. He holds himself very stiffly because of pain in the back. There is pain on pressure over the sacrococcygeal joint and marked tenderness over the spine of the ninth dorsal vertebra. The under surface of the right heel is exquisitely tender. There is considerable watery purulent urethral discharge, a smear of which shows gonococci. The prostate is moderately enlarged. The right seminal vesicle is palpable.

Urine from both anterior and posterior urethra contains pus but no albumin or casts. Gonococcus fixation test is negative. Wassermann reaction is negative. Roentgen ray shows periosteal exostosis of the os calcis of both heels.

His symptoms remained unchanged during the first seven days in the hospital. February 1 he was given intravenously 40 million of the New York City Board of Health typhoid vaccine. On the third, the fifth and the seventh similar doses were given. The character of the reactions following the injections appears on the temperature chart. The chills began from thirty to seventy-five minutes after the injection. On the thirteenth a dose of 50 million was given. On the seventh and thirteenth the patient was observed in the calorimeter. No noticeable improvement resulted from the vaccine therapy. On the first day following each injection he was more stiff and uncomfortable. On the second day the condition returned to that which obtained before the vaccine was given. He was discharged improved.

Case 6.—Frank G., chronic gonococcus arthritis, a barber, born in the United States, 42 years of age, a widower, was admitted Feb. 13, 1917, to the service of Dr. C. E. Nammack, transferred to the Metabolism Ward and discharged unimproved May 8, 1917. He says he has had gonorrhea seven times, the first attack being at the age of 15. He has had three distinct attacks of arthritis, all of which had occurred during or immediately following an acute art..ritis.

During the past year the joint pains have been almost constant. Since January, 1917, he has had a urethral discharge and more severe joint involvement. He has always used alcohol to excess. (During the past month he has consumed as much as a quart of whisky a day). February 16, in another ward, he received intravenously a 20 million dose of New York City Board of Health typhoid vaccine. February 19 he received 30 million. The joint condition was not improved but the urethral discharge, which had been profuse, was checked. He is a poorly nourished, fairly well developed, very dissipated looking man. He has no temperature elevation and does not appear to be toxic. His throat is congested. The tonsils are normal in appearance and his teeth are in fair condition. His spleen is felt two finger breadths below the costal margin. He has moderate pain, tenderness and swelling in the right wrist, right hand and right knee. His prostate is enlarged. Massage of this organ causes the discharge of a drop or two of thin, purulent material which contains large numbers of gonococci.

His gonococcus fixation test is strongly positive. Wassermann is negative.

February 27 he was transferred to the general service. March 10 the urethral discharge again became profuse. March 27 he developed a severe gonorrheal conjunctivitis. He had entirely recovered from this at the time of his discharge May 8. The joint condition, however, was unimproved.

Case 7.—Genaro, A., acute rheumatic fever, a munition factory worker, born in Cuba, 22 years of age, was admitted to the hospital Feb. 25, 1917, and discharged improved March 16, 1917. He says that he has never been ill before. He denies gonorrhea and syphilis.

Since February he has had pain in both knees, wrists, shoulders, elbows and ankles. With it, he has had a slight sore throat, some headache, and at the onset of the illness several nose bleeds. March 26 he received intravenously in another ward a 60 million dose of New York City Board of Health typhoid vaccine; March 27, 50 million; and March 28, 50 million. He had severe reactions in each case. After the first injection there was considerable clinical improvement. The other doses had little or no effect.

Physical Examination.—He is a well nourished and developed Cuban boy of remarkably sanguine disposition in spite of considerable pain. He is not toxic. The tongue is moist. His tonsils are small and not inflamed. The teeth show many fillings and gold crowns. At the time of admission his heart was normal but later there developed a soft, blowing, systolic murmur, maximum at the apex and transmitted outward into the axilla. The spleen is felt one fingerbreadth below the costal margin. The left wrist, elbow and shoulder are painful on motion.

March 2, after receiving a 20 million dose of typhoid vaccine, he was observed in the calorimeter. He had no chill. On the third, fourth and sixth he received a dose of 40 millions. Each time he had a chill with severe reaction. The joint pains gradually improved. Improvement, however, seemed to bear no definite relation to treatment. After the last injection his temperature reached normal and remained so until his discharge March 16. At that time all joint pain and swelling had disappeared but the heart murmur persisted.

In all, eight observations were made, lasting from two to eight and a half hours. When changes in the metabolism were expected the periods were made as short as possible. One period of only twenty-two minutes was obtained. It would have been interesting to subdivide the period of chill but no experimental period can be ended unless the subject has been quiet for six or seven minutes. Short periods are not as accurate as long ones since a small error in determining the

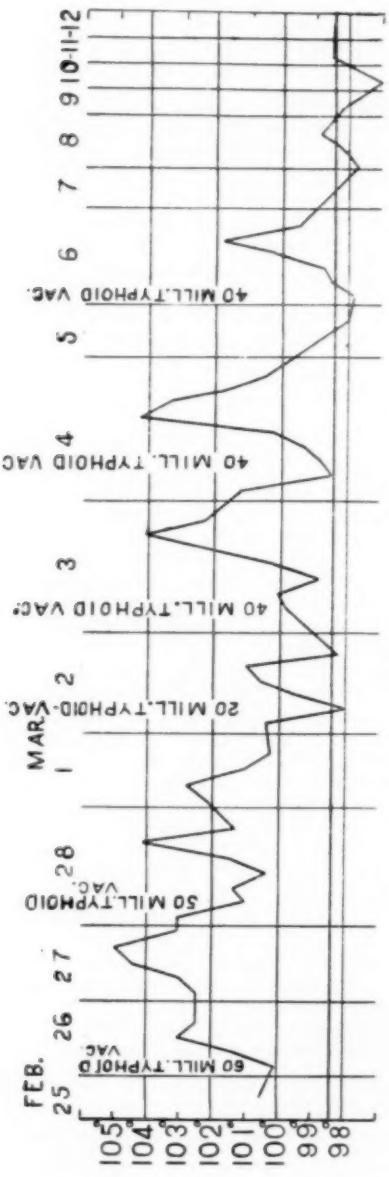

Fig. 2.—Temperature curve of Genaro A.

residual carbon dioxid or oxygen will cause a larger percentage change in the shorter period. This error will, of course, be compensated for in the next period.

The time of the chill never corresponds exactly to the experimental period in which it is observed. It is possible, however, to calculate with fair accuracy the heat production occurring during the chill itself. We may consider that the metabolism during the few minutes before the chill is at the same level as that of the preceding period. Similarly the metabolism in the short interval after the paroxysm approximates the level of the following period. The heat thus calculated for the interval before and after the chill is subtracted from the total heat produced during the entire experimental period. In this manner, the heat production during a twenty minute chill can be estimated even though the experimental period be forty minutes long.

The data of the calorimetric experiments are given in Table 1. Figure 3 shows graphically the results of the calorimeter observation on John B. Figures 4 and 5 show the results on Joseph McC. (Case 5). Figure 6 on Frank G. (Case 6); Figure 7 on William B. (Case 2); Figure 8 on Genaro A. (Case 7).

DISCUSSION OF RESULTS

The phenomena observed after the intravenous injection of foreign protein are almost identical with those observed in malaria.[1] For convenience of discussion the malarial paroxysm was divided into six periods: (a) a basal period before the chill; (b) a prodromal phase immediately before the chill; (c) the chill itself; (d) a period of rising temperature after the cessation of shivering; (e) a period of high continuous temperature corresponding to the clinical stage of heat, and, finally, (f) a period of falling temperature. In considering the reactions to foreign proteins, this same division is useful.

In the chills of malaria, the respiratory quotients were found to be high. The same thing is observed during the chill following the injection of vaccines, which indicates a rapid combustion of the glycogen stores of the body. In most of the experiments, the quotient falls steadily after the chill.

Four main questions of the mechanism of the rise and fall of body temperature will be considered.

1. The relation of heat production to heat elimination as factors in the rise and fall of temperature.

2. The divergence of the rectal temperature from the average body temperature.

3. The relation of heat lost in the vaporization of water to the total heat elimination and to the heat production.

4. The influence of body temperature on heat production.

The data on which the discussion is based are presented in Table 2.

TABLE 2.—SUMMARY OF DATA ON HEAT REGULATION

Name; Date; Surface Area	Condition of Patient	Length of Period	Rectal Temperature, C.	R. Q.	Heat		Per Cent. Divergence of Direct from Indirect, Cal.	Change in Rectal Temperature	Change in Average Body Temperature	Per Cent. Total Heat Elim. Lost in Vap. of Water	Per Cent. Heat Produced Lost in Vap. of Water	Calories per Square Meter per Hour	Per Cent. Rise Above Normal Basal for Age
					Produced Ind. Cal.	Eliminated							
John B. ... 1/2/17 1.75 Sq. M.	Chill	50 minutes	37.8-39.2	0.89	152.5	70.6	— 8.5	+1.4	+1.69	24.1	11.1	105.0	+156
	Rising temperature after chill	30 minutes	39.2-39.9	0.86	48.1	43.2	+58.0	+0.7	+0.10	21.6	19.4	54.8	+ 34
	High continuous temperature	90 minutes	39.9-39.7	0.78	147.5	137.6	—14.7	—0.2	+0.20	20.4	19.2	55.2	+ 35
	Falling temperature	60 minutes	39.7-39.2	0.79	95.4	112.2	— 9.8	—0.5	—0.35	24.5	28.8	54.5	+ 33
Joseph Mc. 2/-/17 1.46 Sq. M.	Afebrile before vaccine	60 minutes	37.5-37.5	0.82	62.4	61.5	— 3.4	±0.0	+0.02	26.5	26.1	42.7	+ 8
	Afebrile after vaccine but before chill	55 minutes	37.5-37.3	0.79	58.2	56.4	—14.4	—0.2	+0.04	28.3	27.4	40.7	+ 30
	Chill	60 minutes	37.3-38.4	0.80	90.3	66.1	+24.0	+1.1	+0.57	28.9	24.9	57.9	+ 49
	Rising temperature after chill	60 minutes	38.4-38.8	0.76	72.1	66.4	+ 9.0	+0.4	+0.13	27.0	19.0	46.2	+ 17
Joseph Mc. 2/12/17 1.46 Sq. M.	Afebrile before chill	52 minutes	37.2-37.1	0.89	51.4	46.9	— 5.7	—0.1	+0.10	21.9	20.1	40 5	+ 3
	Chill	40 minutes	37.1-38.2	0.92	77.1	44.6	+20.0	+1.1	+0.78	23.2	13.4	79 3	+101
	Rising temperature after chill	2 hours	38 2-38.6	0.83	149.0	131.5	— 0.4	+0.4	+0.40	23.3	20.5	51.0	+ 29
	Falling temperature	4 hrs. 20 m.	38.5-37.6	0.83	274.0	304.0	— 2.4	—0.9	—0.58	23.4	25.1	43.9	+ 11
Genaro A. ... 5/2/17 1.56 Sq. M.	Afebrile	30 minutes	37.6-37.6	0.89	33.3	32.1	— 3.9	±0.0	+0.03	23.5	22.7	42.7	+ 8
	Rising temperature without chill	2 hrs. 30 m.	37.6-38.3	0.79	199.1	177.5	+ 3.0	+0.7	+0.49	26.5	23.9	51.5	+ 31
	High continuous temperature	60 minutes	38.3-38.3	0.76	85.8	78.7	—10.8	±0.0	+0.17	27.2	24.9	55.0	+ 39
William B. 1/15/17 1.80 Sq. M.	Rising temperature before chill	40 minutes	37.3-37.6	0.87	68.6	50.1	— 1.7	+0.3	+0.34	26.1	19.1	57.2	+ 53
	Chill	30 minutes	37.6-38.6	0.87	111.2	49.4	— 6.5	+1.0	+1.13	32.1	14.2	123.5	+229
	Falling temperature	60 minutes	39.1-38.6	0.78	88.8	92.5	—29.5	—0.5	—0.07	24.8	26.0	49.3	+ 31
Frank G. ... 2/23/17	Afebrile before chill	30 minutes	37.5-37.4	0.81	33.2	32.8	—10.2	—0.1	+0.01	37.0	36.5	42.6	+ 11
	Chill	60 minutes	37.4-39.1	0.84	120.1	68.6	+26.0	+1.7	+1.09	32.2	18.4	77.0	+109
	High continuous temperature	60 minutes	39.1-39.2	0.82	77.4	74.0	— 1.2	+0.1	+0.07	30.5	29.2	49.6	+ 29
	Falling temperature	60 minutes	39.2-38.9	0.75	80.3	90.6	— 6.3	—0.3	—0.22	23.0	27.2	51.5	+ 34

Relation of Heat Production to Heat Elimination.—In malaria, it was found that during a chill the heat production was enormously increased while the heat elimination remained practically at its basal level. After injection of foreign protein, the same mechanism is observed. It would seem as if the temperature regulation were set at a higher level and that the body responded by producing heat sufficient to warm the tissues to the new temperature level. After

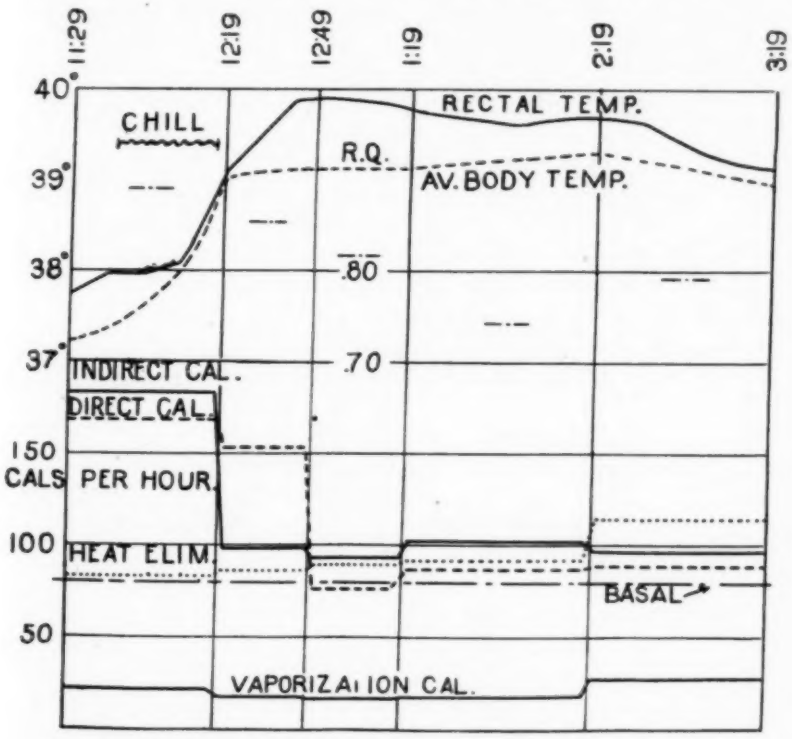

Fig. 3.—Calorimeter observation on John Br., February 2. At 10:50 a. m., 25 million typhoid bacilli were given intravenously. The chill lasted from 11:40 a. m. to 12:10 p. m. The upper curve shows the rectal temperature measured every four minutes; the dash line below shows the change in the average body temperature, as calculated from the difference between heat elimination and heat production as determined by the method of indirect calorimetry. This line is started arbitrarily 0.5 C. lower than the rectal temperature. While it is possible to determine the rise and fall of the average body temperature, it is absolutely impossible to fix the exact level at which these fluctuations take place. After the start at 11:29 a. m., the first satisfactory fixation of this line was at 12:49 p. m. Between these points the exact shape of the curve is not certain. The respiratory quotient (R. Q.) is indicated by short lines in each period. The line at 80.8 calories represents the basal heat production per hour as determined on January 31.

vaccine, the heat production is increased from 75 to 210 per cent. during the chill, while the amount of heat eliminated is scarcely increased above its former basal level. This, of course, results in the storage of large amounts of heat within the body. After the chill is over, the heat production drops sharply but still remains somewhat above the normal, as is usually the case during increased body temperature. The rectal temperature still continues to rise after the shivering ceases. The heat elimination is practically unchanged. During the

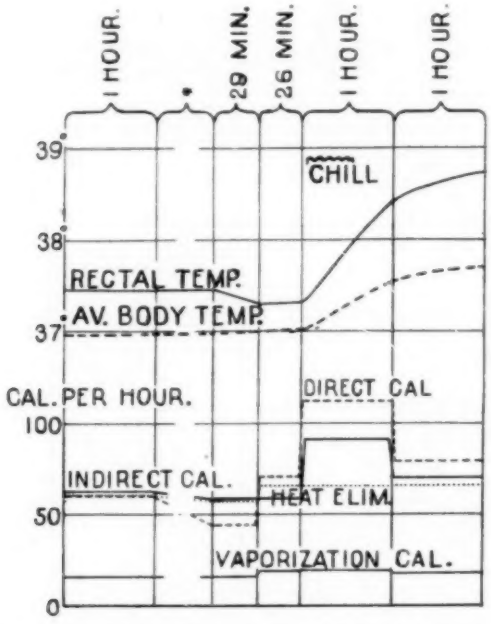

Fig. 4.—Calorimeter observations on Joseph McC., February 7. The first period from 11:09 a. m., to 12:09 p. m., was a basal determination. At 12:31 p. m. he was given an intravenous injection of 40 million typhoid bacilli. Two short periods were obtained before the chill, which lasted from 1:45 to 2:15 p. m. Note that the average body temperature rises more slowly than the rectal temperature.

stage of high continuous temperature the heat elimination increases until it is equal to the heat production; both, however, being at a level from 20 to 40 per cent. above the normal. During the fall in body temperature, the heat production drops gradually to the basal level and the heat elimination increases steadily.

Relation of Rectal to Average Body Temperature.—During the past ten years, more than 300 observations on patients with normal

temperature have been made with the Sage calorimeter. They have shown a remarkably close agreement between the direct and indirect

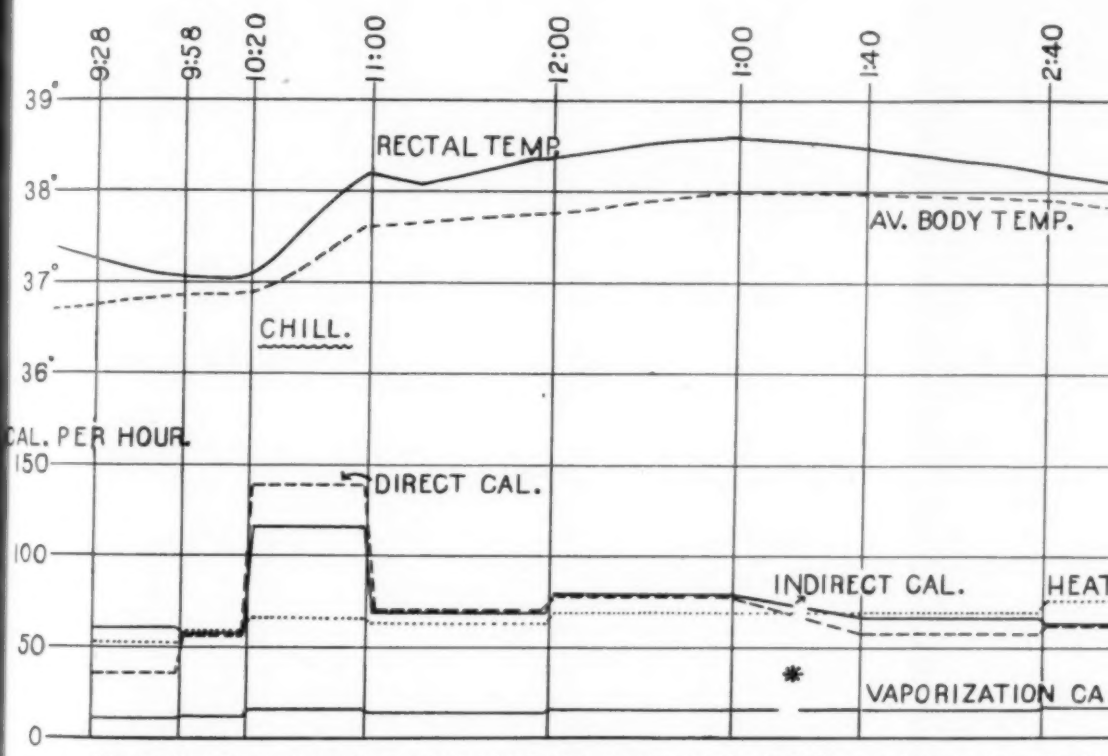

Fig. 5.—Calorimeter observation on Joseph McC., February 12 and 13. At 9:05 p. m. he was given 50 milli from 10:21 to 10:53 p. m. At 1:00 a. m. the calorimeter was opened to give the patient a drink of water. It wa 1:40 a. m. Note that the curve for the average body temperature lags behind that of the rectal temperature.

change more or less than that of the rest of the body.

temperature have been made with the Sage calorimeter. They have shown a remarkably close agreement between the direct and indirect methods of measuring heat production. In patients with fever, however, and particularly in malaria, there has been a wide divergence between the two methods. This may be explained on the following basis. The measurement of heat production by direct calorimetry depends for one of its factors on the rectal temperature which in the

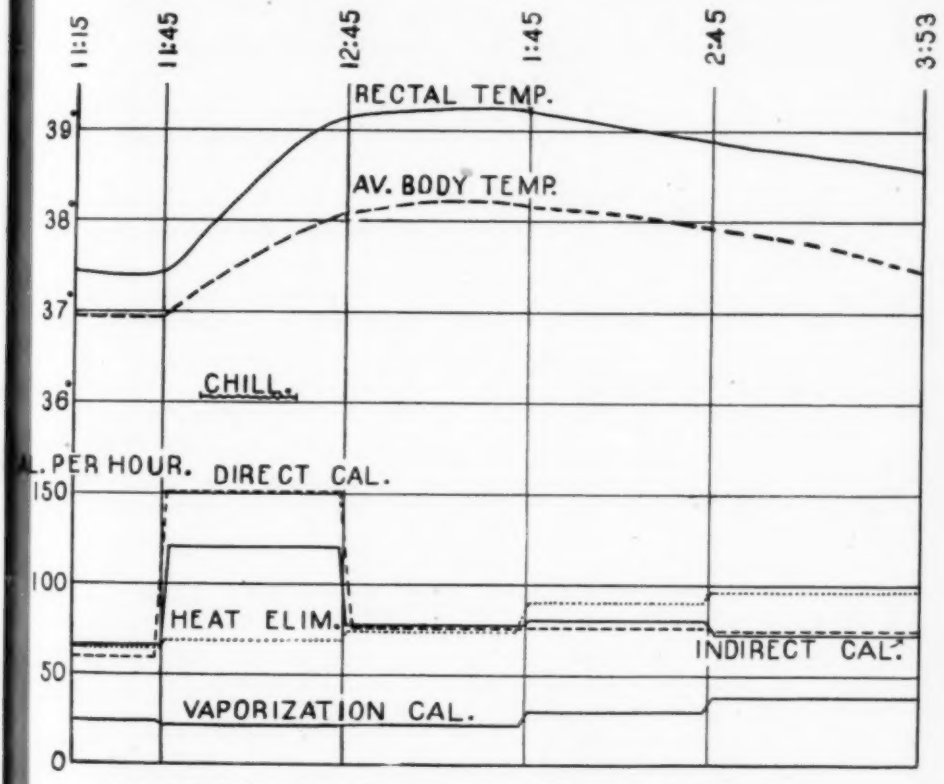

Fig. 6.—Calorimeter observation on Frank G., February 23. At 10:51 a. m. 35 million typhoid bacilli were given intravenously. The chill lasted from 11:58 a. m. to 12:25 p. m. The average body temperature rose less sharply than the rectal temperature.

calculation is assumed to represent accurately the average temperature of the body. During rapid production of heat, such as is seen during a shivering chill, the distribution of heat will not be immediately uniform, with the result that the temperature in the rectum may change more or less than that of the rest of the body.

Exact measurement of average body temperature appears impossible since we cannot have thermometers in all parts of the body. In the paper on malaria, however, an indirect method was devised which allows us to calculate this value. For a given interval the difference

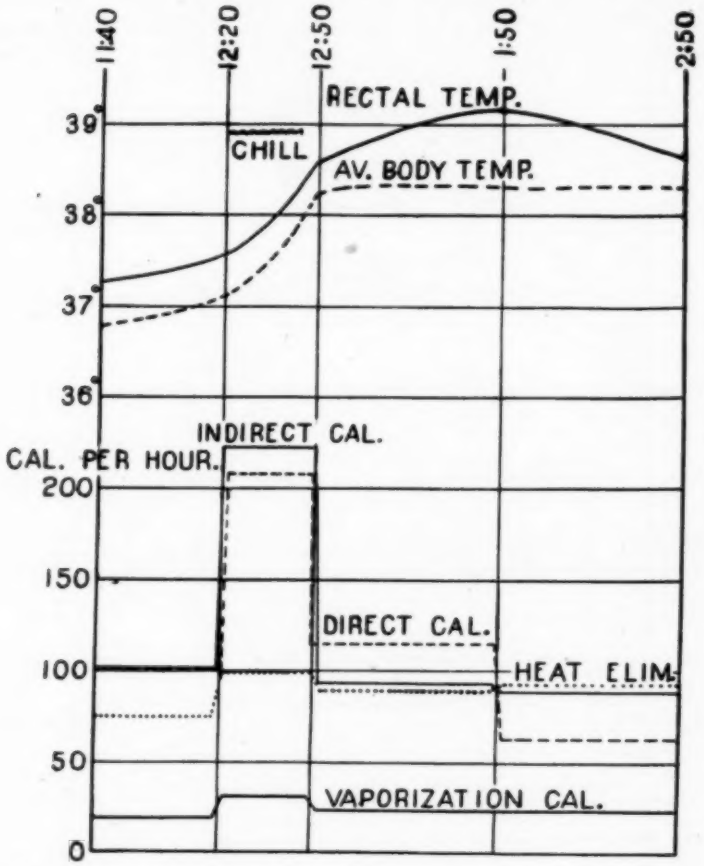

Fig 7.—Calorimeter observation on William B., January 15. At 9:40 a. m. he was given an intravenous injection of 0.8 c.c. of a 4 per cent. proteose solution. He shivered during the last five minutes of the first period and had a violent chill from 12:20 to 12:40 p. m. In this case the average body temperature seems to have risen more sharply than the rectal temperature.

is taken between the number of calories produced, as estimated by the chemical methods of indirect calorimetry and the calories eliminated as measured by the direct physical methods. This represents the heat lost or gained by the whole body. When this difference is divided

by the hydrothermal equivalent of the organism, the gain or loss in average body temperature is obtained. For example, heat production 100 calories, minus heat elimination 60 calories=heat stored 40 calories. In a man weighing 70 kg., the hydrothermal equivalent (heat necessary to raise the temperature of the whole body 1 C.)=58.1 calories.[14] The gain in average body temperature is, therefore, $\frac{40}{58.1}$ = 0.66 C. This may be compared with the change in rectal temperature which has been observed during the corresponding time interval.

In Figures 3 to 8, the average body temperature, as calculated by this method, is plotted with the rectal temperature. In about half of the cases, the two methods agree during the chill. In the others,

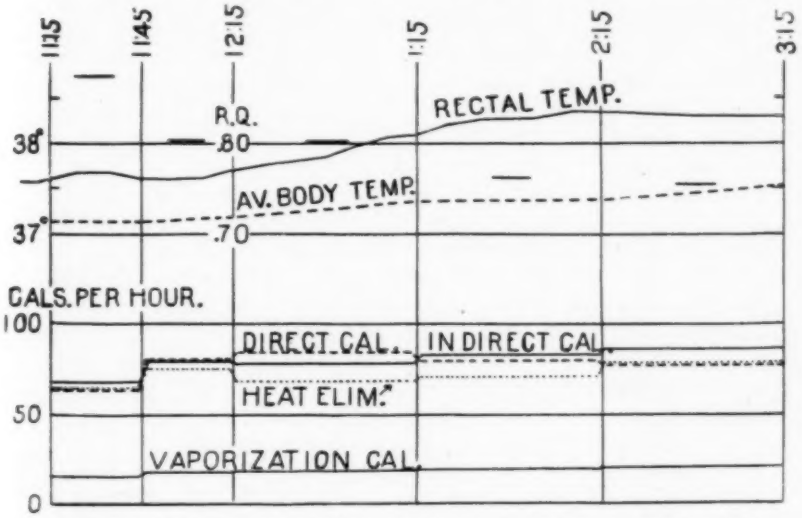

Fig. 8.—Calorimeter observation on Genaro A., March 2. This patient received a small dose of 20 million typhoid bacilli intravenously at 10:50 a. m. He did not have a chill. There was only a slight rise in rectal temperature and even less of a rise in the average body temperature.

the finding is similar to that observed in malaria. The rectal temperature rises more rapidly than the average body temperature. During the period of falling temperature, the heat measurements in the rectum represent with fair accuracy the conditions of the entire body. In the previous discussion of malaria, it was considered that the more rapid rise of rectal temperature indicated a storing of heat in the deeper portions of the body during the chill. In the light of these further observations, however, this cannot be regarded as a con-

14. This value is obtained by multiplying the weight in kg. by the factor 0.83 which is assumed to represent the specific heat of the body.

stant finding. We can only say that, during rapid varations in the production and elimination of heat, the distribution is not always uniform and that the rectal temperature is often an inaccurate index of the average temperature of the body.

The Relation of Heat Lost in the Vaporization of Water to the Total Heat Elimination and to the Heat Production.—Under the constant temperature conditions of the calorimeter, normal individuals accomplish about 25 per cent. of their total heat elimination through the vaporization of water. The same relationship was found in a large number of observations made in afebrile pathologic conditions. With continuous normal temperature, heat elimination and heat production are equal so the calories lost in the vaporization of water also constitutes 25 per cent. of the heat production. During the sharp rise in temperature accompanying chill, we have seen that the heat production is greatly increased while the elimination remains at its normal level. It is conceivable that the heat lost in vaporization might follow either one. In malarial fever, it was found to bear a fairly constant relation to heat elimination. It never followed the curve of rapid fluctuation in heat production. In the present experiments, the same relation is observed (Table 2). During the chill, the calories lost in vaporization constitute a very low per cent. of the heat production. During the fall in temperature, the percentage may be high. The relation to heat elimination, on the other hand, never deviates far from the limits of normal. This is well illustrated in the experiment on John Br. where the heat lost in the vaporization of water varies between 11 and 28.8 per cent. of the heat production while the relation to heat elimination varies only between 20.4 and 24.5 per cent.

The ability of the body to utilize water in heat elimination is of the greatest importance in the regulation of temperature. Because of its high specific heat and fluid character, it is capable of absorbing large amounts of heat from the cells and of distributing it to the surface of the body where it may be eliminated. The dry skin and concentrated urine of acute fevers has often given rise to the belief that the mechanism of heat loss is disturbed.

During exercise, in exophthalmic goiter and in other conditions in which the heat production is increased, the heat elimination increases correspondingly. Wolpert,[15] Benedict and Carpenter[16] and others have shown that during exercise, the heat lost in vaporization is increased not only absolutely but relatively to the total heat elimination.

15. Wolpert: Ueber den Einfluss der Lufttemperatur auf die im Zustand anstrengender körperlicher Arbeit ausgeschiedenen Mengen Kohlensäure und Wasserdampf beim Menschen. Arch. f. Hyg. **26**:32, 1916.

16. Benedict, F. G., and Carpenter, T. M.: The Metabolism and Energy Transformations of Healthy Man During Rest. Carnegie Institute of Washington, Pub. 126, 1910.

Thus, in severe work involving a heat elimination four times the normal amount Benedict and Carpenter found that the calories lost in vaporization constituted 47.6 per cent. of the total. Such findings have been compared with those occurring during fever in which a relative increase in the vaporization calories does not always occur. This is one of the factors which has led Balcar, Sansum and Woodyatt [17] to consider that fever may be due to an inability of the body to mobilize its water reserve for the elimination of heat. It has also been considered an argument for the supposed concentration of blood during fever.

It must be remembered that the rise in heat production involved in even light muscular work greatly exceeds the increase of heat production in fever. Except under conditions of chill, it is unusual to find the metabolism more than 50 or 60 per cent. above the normal

TABLE 3.—COMPARISON BETWEEN EXOPHTHALMIC GOITER AND TYPHOID FEVER IN THE PERCENTAGE OF TOTAL HEAT ELIMINATION LOST IN THE VAPORIZATION OF WATER

Subject	Diagnosis	Date	Heat Production, per Cent. Rise Above Average Normal Basal	Per Cent. Total Heat Elimination Lost in Vaporization of Water	Relative Humidity	
					Beginning	Ending
Morris S.	Typhoid	10/29/13	+41	24	49	49
Edwin T.	Goiter	3/10/15	+39	25	39	40
Charles F.	Typhoid	11/15/13	+37	23	37	47
Max W.	Goiter	4/24/14	+53	20	46	55
		3/23/14	+39	22	39	48
Edward B.	Typhoid	10/23/14	+28	23	41	38
Edwin T.	Goiter	3/ 6/15	+37	25	49	42

level during the course of a fever. It may be more in keeping, therefore, to compare water elimination in fever with some other conditions involving about the same increase in heat production. In Table 3 will be found a comparison of conditions in cases of exophthalmic goiter studied in Paper 14 [18] with those in cases of typhoid fever from Paper 7 [19] of this series. The temperature of the calorimeter was between 23 and 24 C. in all observations. Because the conditions or relative humidity were not always uniform the table is arranged in three groups of two each, showing respectively constant, rising and falling humidity.

17. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

18. Du Bois, E. F.: Clinical Calorimetry, Paper 14, Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**:915 (June) 1916.

19. Coleman, W., and Du Bois, E. F.: Clinical Calorimetry, Paper 7. Calorimetric Observations on the Metabolism of Typhoid Patients with and Without Food, Arch. Int. Med. **15**:887 (June) 1915.

It is to be noted that all percentages in both conditions are close to the average normal value. Max W. with a metabolism higher than any of the fevered typhoid patients lost only 20 per cent. of his calories in the heat of vaporization. The comparison is more striking when one remembers the notoriously moist skin of goiter patients.

In the study of typhoid fever, it was found[20] that during a rising temperature, the percentage of heat lost in vaporization of water was slightly lower than normal. The average was 22 per cent. which must be compared with the average normal of 24 per cent. The variations in the typhoid group, however, were great and the number of cases small. In spite of this, the finding has been considered by others as evidence of the body's inability to mobilize water and hence as a cause of fever. That this is not a constant finding during the rising temperature of fever can be shown in the case of George S., a malaria patient, whose record is shown in Table 4.

TABLE 4.—Relation of Heat Vaporization to Total Heat Elimination in George S., Malarial Fever

Condition	Per Cent. Rise in Heat Production Above Average Normal Basal	Per Cent. Total Heat Elimination Lost in Vaporization of Water
Rising temperature before chill	+ 24	28
Chill	+216	31
Rising temperature after chill	+ 76	31
High continuous temperature after chill	+ 65	29
Falling temperature, profuse sweating	+ 40	36+

It will be seen that the percentage of heat lost in vaporization is well above the average normal not only during the rising temperature but also during the chill and following periods. The same thing is shown even more strikingly in the case of Frank G in Table 2. Similar results were obtained in all observations in erysipelas.

Our data present no evidence that the rise of temperature is dependent on an inability of the body to mobilize its water reserve. It is true that the heat loss in vaporization of water is low when compared with the enormously increased heat production of a chill, but it never falls far below its average normal relation to the total elimination and as in the two cases just cited may rise considerably above it.

The Influence of Body Temperature on Heat Production.—In discussing the conditions in the period following a chill, it was emphasized that the heat production remained from 20 to 40 per cent. above the normal level after shivering had ceased. It was also remarked

20. Soderstrom, G. F., and Du Bois, E. F.: Clinical Calorimetry, Paper 25. The Water Elimination Through Skin and Respiratory Passages in Health and Disease, Arch. Int. Med. **19**:931 (June) 1917.

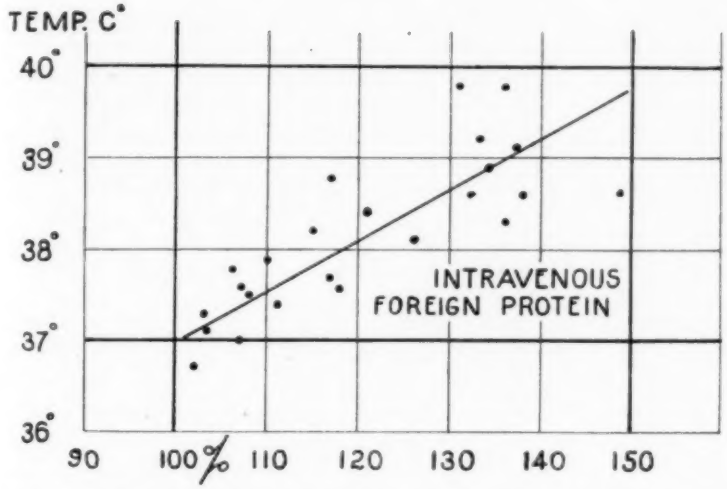

Fig. 9.—Relationship of basal metabolism to temperature in the fever following the injection of foreign protein. Ordinates represent rectal temperature in degrees centigrade, abscissae the metabolism expressed in percentages of the average normal. Each dot represents an experimental period in the calorimeter.

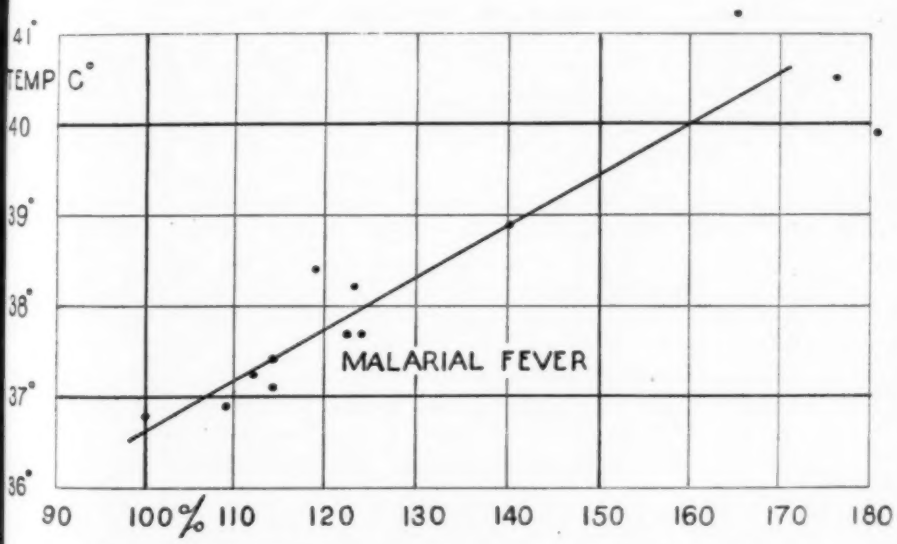

Fig. 10.—Relationship of basal metabolism to temperature in malarial fever.

that this was the usual finding in conditions of increased body temperature. Work on typhoid fever, tuberculosis and malaria has demonstrated that rise in body temperature is accompanied by increased heat production and that the increase corresponds to the degree of fever. Figure 9 shows the relation of heat production to the degree of body temperature after the injection of foreign protein expressed by the method utilized by McCann and Barr [21] in tuberculosis. The ordinates show the rectal temperature in degrees Centigrade. The abscissae show the level of the metabolism in percentage of the average normal. The line 90 means 10 per cent. below the average; 150 means 50 per cent. above the average. Each dot represents a calorimetric observation. Of course, it is necessary to leave out the shivering periods. It is possible that some of the results in the very high temperature following the chill are slightly affected by previous severe muscular exercise. Figure 10 demonstrates the relationships during the fever of malaria. In Figure 11 are grouped in one chart all of the fevers studied. The continued diagonal line is drawn from statistical calculations and the dotted lines are placed to represent divergencies of 10 per cent. in this average. Out of the total of 137 experiments in various fevers, 82 per cent. come within 10 per cent. of the average. In other words, the percentage variations in the metabolism for a given temperature are slightly greater than a similar group of normal individuals.

Most of the patients whose metabolism is very high for the degree of temperature were typhoid or malaria patients with a high level of protein metabolism. Most of those with low basal metabolism were cases of tuberculosis with a normal protein metabolism. We know that protein increases the metabolism through its specific dynamic action and this may explain the difference between the groups of patients. The ingestion of a large protein meal does not increase the heat production in typhoid where the protein metabolism is already high, but it does cause a striking increase in tuberculosis where the protein metabolism is at a much lower level. While the increased protein metabolism seems to be a factor in explaining differences between the various fevers we believe that it is outweighed by another and simpler factor.

The surprising uniformity of results expressed in Figure 11, suggests that we are dealing with a law of the velocity of chemical reactions enunciated by van't Hoff.[22] For ordinary temperatures the van't Hoff law can be expressed as follows: "With a rise in

21. McCann, W. S., and Barr, D. P.: Clinical Calorimetry, Paper 29. The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.

22. van't Hoff, J. H.: Studies in Chemical Dynamics. Revised by E. Cohen. Translated by T. Ewan. Easton, Pa. Chemical Publishing Co., 1896.

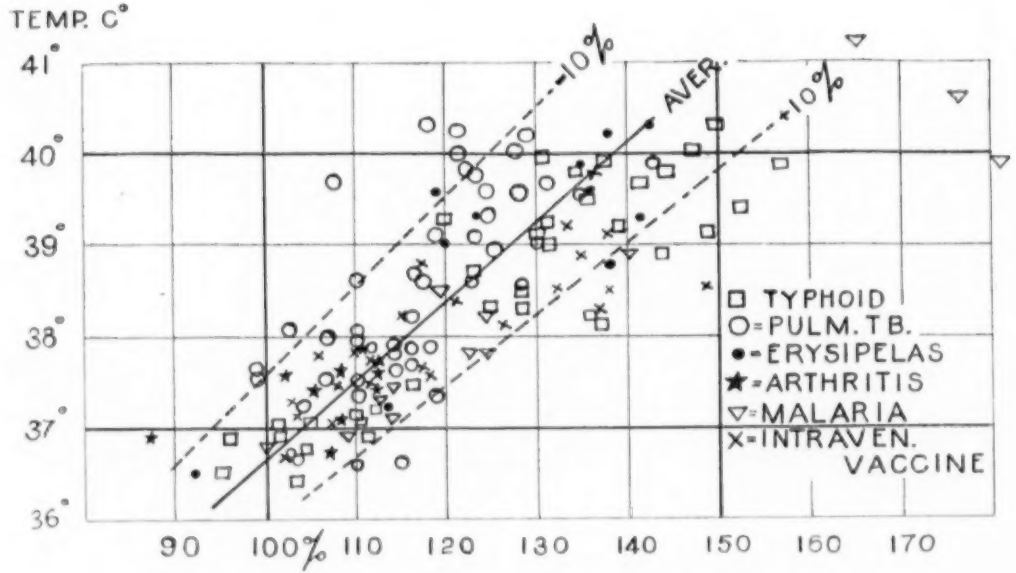

Fig. 11.—Relation of basal metabolism to temperature in six different fevers. The continuous line shows the average and the dotted lines are drawn to represent metabolism 10 per cent. above and 10 per cent. below the average.

temperature of 10 C. the velocity of chemical reactions increases between two and three times." In other words, the temperature coefficient is usually between 2 and 3. This means an increase of from 30 to 60 per cent. for the three degree rise from 37 C. to 40 C. Virtually all of the fever experiments are within these limits and the average line shows a temperature coefficient of 2.3.

Van't Hoff and Kanitz [23] give the temperature coefficients which show the rate of increase in a number of chemical reactions with an equal rise in temperature. If we plot these in exactly the style of the

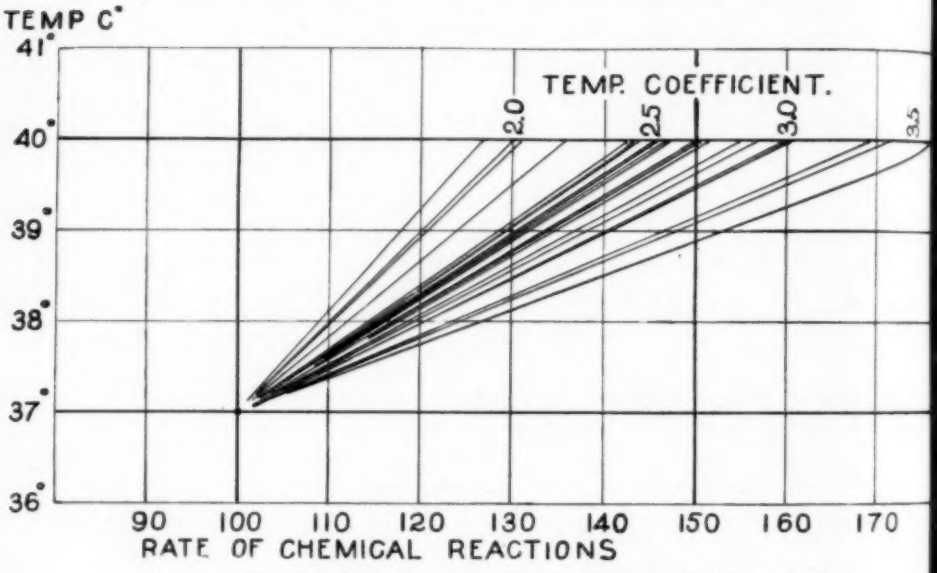

Fig. 12.—The lines in this chart represent a number of typical chemical reactions taken from van't Hoff and Kanitz. The slope of the lines shows the increase in the rate of the reactions as the temperature is raised. Note that the lines correspond closely to those which represent the total oxidations in the human body.

fever patients (Fig. 12) we note that the lines have approximately the same slope. In other words, the reactions in a fever patient respond to a rise in temperature in a manner which resembles closely the chemical reactions in the test tube suspended in a water bath.

There is a tremendous gap between the simple reactions in the test tube and the complex oxidations in the diseased human body and we should hesitate to compare them were it not for the large number

23. Kantiz, A.: Temperatur und Lebensvorgänge in Biochemie in Einzeldarstellungen: Heft 1. Gebrüder Borntträger, 1915, Berlin.

of biologic reactions which show temperature coefficients between 2 and 3. Van't Hoff calls attention to the rate of carbon dioxid elimination in plants which show a coefficient of 2.5. Kanitz gives a long list of similar coefficients for plant respiration, rate of isolated hearts, contraction of smooth muscle and the metabolism in cold blooded animals.

SUMMARY AND CONCLUSIONS

1. Eight calorimeter experiments have been made on subjects after the intravenous injection of proteose and of typhoid vaccine. In five of these it was possible to observe the phenomena of chills.

2. With the onset of a chill there is a sudden increase of from 75 to 200 per cent. in heat production due, in part, to the shivering. At the same time, there is almost no rise in the heat elimination. This discrepancy between production and elimination causes the storage of a large amount of heat within the body. After the chill there is a short period of level temperature when the heat production and heat elimination are equal and both are from 20 to 40 per cent. above the basal level. Following this, as the temperature falls, there is usually a steady decrease in heat production until it reaches the normal level. The heat elimination, on the other hand, increases still farther, thus getting rid of the stored heat. During the falling temperature there is never as large a discrepancy between elimination and production as during the chill.

3. The respiratory quotient tends to be high during the chill, indicating the rapid combustion of the glycogen stores of the body. After the chill, the quotient falls steadily.

4. By means of a comparison of the heat production and heat elimination, it is possible to determine the temperature changes of the body as a whole and compare them with the changes in rectal temperature. The rectal temperature indicates, in a general way, changes in average body temperature, but it is possible to have a rise in rectal temperature while there is a fall in the average body temperature. The opposite is also true.

5. The heat lost in the vaporization of water from the skin and lungs bears a fairly constant relationship to the total heat elimination but has no relationship to the heat production during rapid changes in temperature. Study of the water elimination in fever affords no evidence that the body is unable to mobilize water for heat elimination. Fever should not be attributed to failure in the function of water elimination.

6. Observations in this and in other fevers has demonstrated that rise in body temperature is accompanied by increased heat production the amount of which corresponds to the degree of fever. It is found

that this increase follows van't Hoff's law, which may be stated as follows: "With a rise in temperature of 10 C., the velocity of chemical reactions increases between two and three times."

7. The phenomena of the chill following intravenous injection of proteose or vaccine are strikingly similar to those of the malarial paroxysm, the method of temperature regulation being almost identical.

A CORRELATED STUDY OF THE INDICATIONS FOR TONSILLECTOMY AND OF THE PATHOLOGY AND BACTERIOLOGY OF THE EXCISED TONSILS*

LEONORA HAMBRECHT, B.S., AND FRANKLIN R. NUZUM, M.D.
SANTA BARBARA, CALIF.

Careful studies of the flora of the tonsils and of the nasopharyngeal cavities have been made. The discovery of hemolytic streptococci is stressed as the most important bacteriologic finding. They are reported as present in approximately 50 per cent. of throats with extreme variations of from 10 to 100 per cent. In the nasopharynx they have been found less frequently and in smaller numbers. The importance of virulent hemolytic streptococci being the causative agent of many clinical conditions is well established. The rôle of these organisms as secondary invaders in postinfluenzal pneumonia, empyema, etc., is recognized. Also the ability of these bacteria to produce lesions in the stomach, gallbladder, appendix and endocardium; these lesions being secondary to primary foci of infection in the tonsils, teeth, etc., is stoutly affirmed by many. Therefore, the rôle played by streptococci in disease processes is an important one.

The steady progress that has been made in recent years in classifying the large and heterogeneous group of streptococci has given an added interest to the relation of the various strains of these organisms to clinical conditions. It has been demonstrated that several strains are homogeneous, that they have definite cultural characteristics, sugar reactions and agglutinin and precipitin properties. The association of certain strains with specific clinical conditions is now proved. Of the eight groups of hemolytic streptococci in Holman's classification,[1] four are known to be of frequent occurrence and closely related to septic disease processes and the remaining four are apparently nonpathogenic and of infrequent occurrence. Progress has also been made concerning the relation and the clinical significance of Holman's eight subgroups of nonhemolytic streptococci.

Likewise, the pathology of excised tonsils has been studied carefully and the changes which occur as the result of local infection are well known.

But while each phase of the relationship between the clinical indication for the removal of the tonsils, the pathology of the excised tonsils, and the predominating organism recovered, has been recorded

* From the Laboratories of the Santa Barbara Cottage Hospital.

1. Holman, W. L.: Classification of Streptococci, J. M. Research **28**:377, 1916.

many times by independent workers, the three phases have not been frequently worked out on the same material.

With this in mind we have tabulated the clinical indications for tonsillectomy in 218 patients. We have noted the pathologic changes in the excised tonsils. In studying the bacterial flora we have compared the results obtained by making cultures from the surface of the tonsil and, after cutting the tonsil with a sterile knife, with the cultures made from the depths of crypts. In tabulating the streptococci found, we have used the classification of Smith and Brown,[2] which divides these organisms into the hemolytic alpha, alpha prime, and beta groups and into the nonhemolytic gamma group. In deep colonies in poured blood agar plates which are not too thickly seeded the alpha group has a green area of discolored corpuscles immediately about the colony, outside of which there may or may not appear a partially hemolyzed zone. If the petri dish containing such colonies is placed in the icebox for twenty-four hours, the hemolyzed zone about the colony may become more clearly defined. Outside of this zone a second zone of greenish discoloration may develop, and beyond this another zone of hemolysis. If such a culture is alternately incubated and refrigerated as many as four zones may develop. Pneumococci resemble this group so closely that we have determined their solubility in bile, in order to accurately identify the colony. The alpha prime group of hemolytic streptococci have in deep cultures a faint haze immediately about the colony, due to incomplete hemolysis. The colonies of the beta group are surrounded by a sharply defined zone of complete hemolysis which varies from 1 to 5 mm. in diameter. The gamma group produces no hemolysis.

Method.—In order to obtain comparable results, we have followed the cultural methods suggested by Brown,[3] using beef extract and Digestive Ferments Co. peptone, the agar having a reaction of 0.5 per cent. normal acid to phenolphthalein. Twelve c.c. of this was mixed with 0.5 c.c. of human blood. Such a medium is very suitable for studying the various types of hemolysis. With a sterile loop material from the crypts was placed in about 2 c.c. of sterile physiologic solution of sodium chlorid from which emulsion the blood agar was inoculated, poured into Petri dishes and incubated. The plates were read at the end of twenty-four and forty-eight hours, then they were placed in the icebox for twenty-four hours and again read. The low power of the microscope was used in studying the type of hemolysis about the colony.

---

2. Smith, T., and Brown, J. H.: A Study of Streptococci Isolated from Certain Presumably Milk-Borne Epidemics of Tonsillitis Occurring in Massachusetts in 1913 and 1914, J. M. Research **31**:445, 1915.

3. Brown, J. H.: The Use of Blood Agar for the Study of Streptococci. Monograph, Rockefeller Inst. M. Research, No. 9, p. 40.

Single colonies were fished from Petri dishes, streaked on blood agar slants and the latter incubated. On obtaining a pure culture, the bile solubility of the organism and its sugar reactions were determined in those instances in which it was necessary.

Results.—Of the patients in this group of 218, 60 per cent. were children, 40 per cent. adults. Sixty-three per cent. gave a history of repeated sore throat. Frequent colds, together with enlargement of the tonsils were recorded in 14 per cent. Eight per cent. complained of mouth breathing. Eight per cent. had a history of one or more attacks of rheumatism. Seven per cent. had otitis media, and tonsillectomy was done in an endeavor to improve this condition.

Microscopic study of the entire number of tonsils removed revealed definite pathologic changes in 93 per cent. Seven per cent. were regarded as normal. In classifying the type of change we have followed the plan used by Moore,[4] i. e., chronic lacunar tonsillitis, chronic interstitial tonsillitis, and chronic peritonsillitis. We have classified separately those instances that presented gross or microscopic abscesses and those in which lymphatic hyperplasia was the only change noted (Table 1).

TABLE 1.—PERCENTAGE OF INSTANCES IN WHICH THE VARIOUS CHANGES WERE NOTED

Pathologic Condition	Percentage
Chronic lacunar tonsillitis	42
Chronic interstitial tonsillitis	21
Chronic peritonsillitis	6
Abscesses	10
Lymphatic hyperplasia as the only change	14
Mucous glands in capsule	7
Cartilage in capsule	3

Forty-two per cent., or nearly one-half of the entire number, presented changes in the lining epithelium of the crypts and its immediate neighborhood. In many, these crypts were filled with debris. The epithelium itself was quite frequently necrotic and microscopic abscesses just beneath the crypt epithelium were common. In the 21 per cent. of instances in which chronic interstitial changes were noted, there was a marked increase in the connective tissue stroma of the tonsil, representing a chronic inflammatory reaction. In the five per cent. of tonsils that had peritonsillar involvement the changes as described about the crypts and the connective tissue frame work were usually present to some degree but the evidence of infection and of repeated inflammation were especially pronounced in the thickening and hyperplasia of the capsular tissue.

The tonsils of the patients with a history of many attacks of tonsillitis, or of rheumatism, or of frequent colds, of mouth breathing, of otitis media, presented certain pathologic changes.

4. Moore, J. J.: Chronic Tonsillar Infections, J. Lab. & Clin. Med. **3**:283, 1917.

In Table 2 it will be noted that in 53 per cent. of the patients who had attacks of tonsillitis, the pathologic changes in the tonsil were most marked about the crypts, that is, the so-called chronic lacunar tonsillitis. Fourteen and four tenths per cent. of these had an associated lymphatic hyperplasia. The next most frequent change in this type of tonsil was the chronic interstitial tonsillitis present in 17.7 per cent., while peritonsillitis and abscesses were present in 8 and 4 per cent., respectively. The tonsils of the patients with a rheumatic history presented chronic interstitial change in 66.6 per cent. and peritonsillar change in 33 per cent. In 16 per cent. of these tonsils abscesses were found. Of the patients complaining of frequent colds, 58 per cent. had a lymphatic hyperplasia, and of those complaining of mouth breathing 100 per cent. presented this change. In these patients the adenoid tissue was also increased in amount.

TABLE 2.—Pathologic Changes in Tonsils in Various Conditions

Pathology	Attacks of Tonsillitis, per Cent.	Rheumatism, per Cent.	Colds, per Cent.	Mouth Breathing, per Cent.	Otitis Media, per Cent.
Chronic lacunar tonsillitis	53.0	16.6	33.3	...	50
Chronic interstitial tonsillitis	17.7	66.6	16.6	...	..
Chronic peritonsillitis	8.0	33.0	....	...	..
Abscesses of tonsils	4.0	16.0	....	...	..
Lymphatic hyperplasia	14.4*	....	58.3	100	50

* In association with other changes.

The bacteriologic findings, using Smith and Brown's classification, are interesting from many standpoints. The results of other workers using either the streaked plate or the poured plate method are so variant that we have used both methods simultaneously. We have thus been able to contrast the findings and to judge fairly of the worth of each method (Table 3). Without specifically subdividing the hemolytic streptococci into alpha, alpha prime or beta groups we have the following:

TABLE 3.—Bacteriologic Findings

	Streaked Plate Method, per Cent.	Poured Method, per Cent.
Hemolytic streptococci, all types	45.0	96.1
Nonhemolytic streptococci	3.5	2.6
Staphylococcus	64.0	37.0
Pneumococcus	18.0	40.8
Bacilli	7.0	1.9

Comparing these tables the great diversity in the results obtained is apparent. Using poured plates, hemolytic streptococci and pneumococci were found twice as frequently, whereas staphylococci in reportable numbers were found less than one-half as frequently as in streaked plates. By the latter method certain rapidly growing organisms, such

as the staphylococcus, obscured other and often more important organisms. Hemolytic staphylococci prohibited the recognition of other hemolytic organisms. The various groups of hemolytic streptococci were recognized with difficulty and uncertainty by the streaked method and were frequently missed altogether. We have also noticed that on a streaked plate the hemolytic beta group often completely obliterated the alpha, the alpha prime, or the gamma type even when the latter are present in numbers.

The findings explain the wide difference in the percentage of various organisms in tonsil reports by other workers, some of whom used one method and some the other. To us it is sufficient evidence that for accurate results the poured plate must be used.

The hemolytic streptococci which were present in 96.1 per cent. of the 218 tonsil examinations were classified according to the type of hemolysis. Colonies of the alpha type were present in notable numbers in 25 per cent. of instances, alpha prime in 32 per cent. and beta in 86.1 per cent.; all three of them frequently occurring in a single culture from the same tonsil. The beta group was further subdivided into those of wide and of narrow zone of hemolysis. Those classified as of the narrow zone had a diameter of 1 mm.; the wide zone had an average diameter of 4 mm. Since most beta hemolytic streptococci fall into one of the two groups, the narrow zone group representing 36.8 per cent. and the wide zone 73.4 per cent., we attempted to demonstrate that this small or wide zone characteristic was a fixed thing and warranted a further subdivision of the beta group.

Both groups were found to be pathogenic for rabbits (1 c.c. of a twenty-four-hour bouillon culture). We then routinely inoculated the test sugars with wide and narrow zone cultures and fermentation has uniformly resulted as shown in Table 4.

TABLE 4.—DIFFERENTIATION OF STREPTOCOCCI ACCORDING TO ZONE PRODUCTION IN CULTURE

	Saccharine	Lactose	Raffinose	Salicin	Mannite	Inulin
Wide zone	+	+	0	+	0	0
Narrow zone	+	+	0	+	0	0

Since there had been no difference in the reactions of the sugars and since both were pathogenic for rabbits, the permanency of the characteristic of a wide or narrow zone of hemolysis became of special interest. Clawson found hemolysis constant in a series of 134 strains even after two years. Brown [5] recorded some loss of hemolytic activity for certain strains. This loss always took the form of slightly smaller

5. Brown, J. H.: The Use of Blood Agar for the Study of Streptococci, Monograph, Rockefeller Inst. M. Research, No. 9, p. 81.

zones after a period of from fourteen months to two years. He never noted a transition from the beta to the alpha types or vice versa and concluded that the permanence of the apparently minor characteristics of all the strains studied is surprising. Anthony [6] also found only a slight variability in the hemolytic power of streptococci. It being the consensus of opinion that hemolytic characteristics of streptococci are constant, we felt that very possibly beta hemolytic streptococci could be divided into wide and narrow zone groups. However, this characteristic of a wide or narrow zone of hemolysis was found to vary frequently on subculture. A culture from a single colony of a wide or a narrow zone organism often gave colonies with both wide and narrow zones of hemolysis. This occurred so frequently that we felt that the evidence was not at hand to warrant a subdivision of this group. It would seem that the variation in the extent of hemolysis has to do with an extra cellular streptolysin, a substance which has been demonstrated in cultures of hemolytic streptococci and which is a common property of the members of this group.[7] The amount of hemolysis apparently depends on the amount of streptolysin produced.[8]

A detailed study of the organisms isolated from the excised tonsils of patients with various complaints such as tonsillitis, rheumatism, etc., was made. The findings are recorded in Table 5.

TABLE 5.—Organisms Isolated from Excised Tonsils

	Alpha, per Cent.	Alpha Prime, per Cent.	Beta, per Cent.	All Types Hemolytic Streptococci, per Cent.	Gamma, per Cent.	Pneumococci, per Cent.	Staphylococci and Other Organisms, per Cent.
Tonsillitis	5.0	2.5	76.0	83.0	1.5	5.0	10.0
Mouth breathing	11.0	....	81.0	92.0	....	8.0	....
Frequent colds	8.0	10.0	61.0	79.0	....	10.0	11.0
Otitis media	....	....	100.0	100.0	....	....	....
Rheumatism	18.5	....	54.5	73.0	9.0	9.0	9.0
Pathologic tonsils	8.5	2.5	74.5	85.4	2.1	6.4	6.0
Normal tonsils	14.0	....	14.0	28.0	....	14.0	58.0

Following tonsillitis the predominating organism was a hemolytic streptococcus in 83 per cent., the pneumococcus in 5 per cent. and staphylococci and other heterogenous organisms in 10 per cent. Nonhemolytic organisms predominated in only 1.5 per cent. Of the hemolytic organisms, the beta group were present in 76.3 per cent., the alpha group in 5 per cent. and the alpha prime in 2.5 per cent. As a contrast, tonsils from patients with rheumatism had as the predominating organism beta hemolytic streptococci in only 54.5 per cent., the alpha or *Streptococcus viridans* group in 18.5 per cent. and non-

6. Anthony: Some Characteristics of the Streptococci Found in Scarlet Fever. J. Infect. Dis. **6**:332, 1909.

7. Ruediger, G. F.: The Production and Nature of Streptocolysin. J. A. M. A. **41**:962 (May 12) 1903.

8. Braun, H.: Ueber das Streptolysin. Centralbl. f. Bakteriol. **62**:383, 1912.

hemolytic streptococci, pneumococci and staphylococci in 9 per cent., each. The alpha or *Streptococcus viridans* group was present in a higher percentage in these tonsils than in any other. This coincides well with clinical findings, this type of organism having a close relationship to rheumatism. Patients with otitis media had beta streptococci as a predominating organism in 100 per cent. The ear discharge had the same organism. Mouth breathing patients whose tonsils presented lymphatic hyperplasia harbored hemolytic streptococci in 92 per cent. and pneumococci in 8 per cent. Patients complaining of frequent colds and whose tonsils also presented lymphatic hyperplasia, had as the predominating organism beta hemolytic streptococci in 61 per cent., alpha streptococci in 8 per cent., alpha prime in 10 per cent., pneumococci in 10 per cent. and staphylococcus and other incidental organisms in 11 per cent.

Taking all of the pathologic tonsils as a group, hemolytic streptococci were present in 96.1 per cent. In 85.4 per cent. they were present as the predominating organism. Taking the bacteriologic findings of the 7 per cent. of normal tonsils in this series hemolytic streptococci of all types were present in only 28 per cent., pneumococci in only 14 per cent. and staphylococci and heterogeneous organisms in 58 per cent. Granting that this is too small a number of normal tonsils on which to base conclusions, yet it is apparent that hemolytic streptococci are present in a higher percentage in pathologic tonsils. This high incidence of hemolytic streptococci is in keeping with the findings of Davis,[9] Pilot and Pearlman [10] and others, though it is considerably higher than many other investigators have recorded. The latter, however, in many instances did not use the poured plate method.

We have made cultures from the crypts of excised adenoid tissue in eighty-four instances. The bacteriologic findings followed so closely the findings of the tonsil culture in the same patient that a separate table did not seem warranted. As a rule, the number of organisms in the adenoid tissue was much smaller than in the tonsil.

SUMMARY

Of 218 persons said clinically to need a tonsillectomy, microscopic examination of these tonsils gave evidence of pathology in 93 per cent.: 7 per cent. were normal.

Of these 218 persons, 63 per cent. gave a history of repeated "sore throats," 14 per cent. of frequent colds and were told that they had enlarged tonsils, 8 per cent. complained of mouth breathing, 8 per cent. of rheumatism and 7 per cent. of otitis media.

9. Davis, D. J.: Hemolytic Streptococci, J. A. M. A. **72**:319 (Feb. 1) 1919.
10. Pilot, I., and Pearlman, S. J.: Bacteriologic Studies of the Upper Respiratory Passages, J. Infect. Dis. **29**:47, 1921.

Chronic lacunar (crypt) tonsillitis was the most frequent pathologic condition found. It occurred in 42 per cent. Chronic interstitial tonsillitis was present in 21 per cent., chronic peritonsillitis in 6 per cent., gross or microscopic abscess in 10 per cent. and lymphatic hyperplasia as the only change in 14 per cent.

Following repeated attacks of tonsillitis, changes in the tonsils occurred most often about the crypts (42 per cent.). In tonsils from patients with a history of rheumatism, chronic interstitial tonsillitis was present in 66 per cent., chronic peritonsillitis in 33 per cent.

The organisms most frequently isolated from these tonsils were hemolytic streptococci. They were present in 96.1 per cent. of all tonsils and were the predominating organism in 85.4 per cent.

The hemolytic streptococci were further subdivided into alpha, alpha-prime, and beta groups and were present in 25 per cent., 32 per cent. and 86.1 per cent., respectively.

Hemolytic streptococci were present in a much higher percentage (96.1 per cent.) in the pathologic tonsils of our group than in the normal tonsils (28 per cent.).

In nearly every instance the same organisms were isolated from the adenoid tissue as from the tonsils of that patient.

Ring formation, as described by Brown, occurred only with the alpha group of hemolytic streptococci and in 5 per cent. of the total number of the alpha cultures.

Avirulent diphtheria bacilli were isolated but three times in the entire series.

By using both the streaked plate and the poured plate method of culture and comparing the results, we have found the latter much more accurate and satisfactory.

BLOOD PIGMENT METABOLISM AND ITS RELATION TO LIVER FUNCTION *

CHESTER M. JONES, M.D.
BOSTON

The exact mechanism involved in the metabolism of the blood pigments, and the precise relation of the liver to these processes, are still but imperfectly understood. Certain theories, however, concerning blood pigment metabolism are very generally accepted. The pigments of the bile have long been believed to be derivatives, in part at least, of hemoglobin. The work of Eppinger and Charnas,[1] Wilbur and Addis,[2] Robertson,[3] Schneider,[4] Hansmann and Howard,[5] Giffin, Sanford and Szlapka,[6] and others has shown that excessive degrees of red cell destruction are accompanied by an increased elimination of bile pigments. Most observers agree that the liver is the main agent concerned in these metabolic changes. However, the lower bile pigments, principally urobilin and urobilinogen, have been supposed to be formed independently of the liver, by the action of bacteria in the lower intestine, on the bilirubin of the bile. The recent work of Hooper and Whipple [7] on dogs with biliary fistulae has made necessary a modification of previous theories. These investigators question the intestinal production of urobilinogen and urobilin, and the absorption of these pigments from the portal circulation. They suggest that the liver itself is capable of forming these substances. They also prove that bilirubin can be formed in various parts of the body without the intervention of the liver, and conclude that normally the liver may be only one of several agents in the process of hemoglobin metabolism.[8] Furthermore, they produce evidence that red cell destruction, with the consequent liberation of hemoglobin, is not the only factor in the production

* From the Medical Services of the Massachusetts General Hospital.

* This paper is No. 25 of a series of articles on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed from a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1. Eppinger and Charnas: Arch. f. klin. Med. **78**:387, 1913.
2. Wilbur and Addis: Arch. Int. Med. **13**:325 (March) 1914.
3. Robertson, O. W.: Arch. Int. Med. **15**:1072 (June) 1915.
4. Schneider, J. P.: Arch. Int. Med. **17**:32 (Jan.) 1916.
5. Hansmann and Howard: J. A. M. A. **73**:1262 (Oct. 25) 1919.
6. Giffin, Sanford and Szlapka: Am. J. M. Sc. **182**:562, 1918.
7. Hooper and Whipple: Am. J. Physiol. **40**:332, 1916.
8. Whipple and Hooper: J. Exper. M. **17**:612, 1913.

of bile pigments. Dietary changes [9] and various drugs [10] are able to cause marked alterations in the elimination of pigments in the bile.

The resynthesis of the bile pigments to hemoglobin is a further property usually attributed to the liver. At present it is generally believed that the liver is able in some way to build up the lower pigment fractions into the more complex molecule of hemoglobin. However, evidence is lacking on this point, as well as to the manner in which hemoglobin becomes incorporated in the red corpuscles.

It is the purpose of this paper to present certain evidence regarding the normal and abnormal physiology of blood pigment metabolism in man, and to demonstrate, if possible, a further relation between the liver and such processes.

METHOD

The introduction of "biliary drainage" by Lyon,[11] in 1919, has provided a method by means of which a more systematic clinical study of the duodenum and biliary tract is permitted than was previously possible. Lyon claims that a solution of magnesium sulphate introduced through the duodenal tube relaxes the sphincter of Oddi, and thus a free flow of bile into the duodenum is obtained. Furthermore, Lyon believes, following Meltzer's [12] theory of contrary innervation, that the magnesium sulphate causes a contraction of the gallbladder musculature, with a resulting flow of gallbladder contents into the duodenum. Following the flow of dark gallbladder bile Lyon obtains a flow of lighter colored bile which he believes is derived from the upper biliary radicles and liver. Lyon thus attempts, after the use of magnesium sulphate, to divide the bile drainage into three fractions, "A," "B" and "C," which are supposed to contain respectively bile from the common duct, gallbladder and liver. By a study of the gross color, certain other physical characteristics, the sediment and the bacteriology of these fractions, Lyon believes it possible to diagnose and localize pathology existing in the duodenum and various portions of the biliary tract.

Although Lyon presents clinical data which are quite consistent with his assumptions, nevertheless definite experimental proof that magnesium sulphate, when introduced into the duodenum, causes a contraction of the gallbladder is conspicuously lacking. The exact action of the salt in the duodenum has yet to be determined. There is a certain amount of evidence that the relaxation of the sphincter of the common bile duct may not be accompanied by contraction of the

9. Hooper and Whipple: J. Exper. M. **23**:137, 1916.
10. Bauer and Spiegel: Deutsch. Arch. f. klin. Med. **1**:129, 1919.
11. Lyon, B. B. V.: J. A. M. A. **73**:980 (Sept. 27) 1919.
12. Meltzer, S. J.: Am. J. M. Sc. **153**:469, 1917.

gallbladder walls. Chrohn, Reiss and Radin [13] were unable to prove experimentally the existence of such a contrary innervation, although they apparently believe that the so-called "B" bile contains gallbladder contents. Einhorn [14] claims that various salts produce a flow of "B" bile into the duodenum. This assumption is undoubtedly correct, although magnesium sulphate produces more constant and better results than other salts. Einhorn further concludes from his experiments that the flow of "B" bile is not due to a flow of bile from the gallbladder into the duodenum, but that it is due merely to stimulation of liver cells to increased activity, with a resulting excretion of bile pigment in increased concentration. This conclusion, however, is based on crude quantitative estimations of pigment values, and is probably incorrect. Careful determinations of the bile pigments in a series of fractions taken before and after the use of magnesium sulphate, in a number of cases in which there was known to be no flow of bile possible from the gallbladder, either on account of a previous obstruction of the cystic duct, or on account of a previous cholecystectomy, tend, by comparison with a series of normal cases, to disprove Einhorn's conclusions. Further reference will be made to these determinations in a later portion of this paper.

For practical consideration, in spite of the fact that experimental work is still lacking as to the exact source of the "B" bile, it seems expedient to assume that it is made up, in part, of bile from the gallbladder. It is highly probable that a solution of magnesium sulphate, when instilled into the duodenum, accomplishes two things. First, it relaxes the sphincter of the common bile duct and causes a free flow of bile into the duodenum. Second, it probably causes a slight contraction of the gallbladder musculature, with the result that some bile from that organ is mixed in with the bile proceeding down the common duct. The result is a mixture of duct, liver and gallbladder bile.

Bile pigments in the duodenal contents have received but slight attention. Schneider,[4] in 1916, and subsequently others, have made quantitative estimates of the bile pigments of the duodenal contents, using a spectroscopic method. These observers concluded that in those cases in which it is generally considered that increased blood destruction is taking place the excretion of bile pigments is also increased. Schneider attempted to show a definite relation between the level of the bile pigments in the duodenum and the actual degree of hemolysis obtaining in any given case. Eppinger, Wilbur and Addis, Robertson, and others had previously obtained high pigment value in similar instances, by making bile pigment determinations of the stools. Hans-

13. Crohn, Reiss and Radin: J. A. M. A. **76**:1567 (June 4) 1921.
14. Einhorn, M.: New York M. J. **113**:313, 1921.

mann and Howard compared the method of estimating the pigments in the stools with the estimations based on the duodenal contents. Figures obtained by either method gave relatively high pigment values in those cases in which increased hemolysis was apparently taking place. Their findings were confirmatory of results obtained by Wilbur and Addis, but Hansmann and Howard do not believe that estimates based on duodenal contents run exactly parallel to those obtained from stool examination. Hansmann and Howard, however, believe the stool method to be more correct. Examination of duodenal contents seems, nevertheless, the more logical method of study. Such a method allows a study of the bile before the pigments have become diminished or altered by action of the intestinal bacteria. Furthermore, analyses based on estimation of bile pigments in the duodenal contents are performed more easily than similar determinations on the stools and are not subject to errors due to such variable factors as constipation, diarrhea, etc.

Lyon's method of obtaining a continuous flow of bile offers a distinct advantage over the method employed by Schneider and others, in which determinations were based entirely on single specimens. Single specimens, in the present studies, were subject to the greatest variations, on account of the intermittent flow of bile from the common bile duct, and on account of various other factors such as salivary, gastric and pancreatic secretions, which introduced errors by causing a dilution of the pigment content in the duodenum.

The technic used in this series of cases consisted in the introduction of the duodenal tube, and the collection by siphonage of duodenal contents in six fractions. These six fractions were collected over fifteen minute intervals, two fractions being taken from the fasting duodenum prior to the introduction of a 33 per cent. solution of magnesium sulphate, and four immediately following the use of the salt. The entire collection of duodenal contents thus covered a period of about one hour and a half.

The duodenal tube was retained over a period of from two to three hours in the majority of cases, depending on the length of time necessary for the tip to reach the duodenum. The exact location of the tube in the duodenum was determined by fluoroscopic examination in the majority of cases. Atropin sulphate, given before the introduction of the tube, practically eliminated any undue flow of saliva. The use of magnesium sulphate provided a nearly continuous and concentrated flow of bile into the duodenum and minimized the errors caused by the flow of gastric and pancreatic secretions. The objection might be raised that atropin might of itself introduce an error, by causing individual variations in the output of bile. Atropin does cause a slight

diminution in the excretion of bile by the liver cells.[10] This diminution is, however, very slight and in the cases studied the administration of the drug caused no appreciable effect in the flow of bile into the duodenum.

Bile pigments were estimated by Wilbur and Addis' method of spectroscopic examination, for each of the six fractions. This method consists essentially in dissolving the urobilinogen, urobilin and other lower bile pigments in a saturated alcoholic solution of zinc acetate, and then determining the pigment content by the spectroscope. The number of dilutions necessary to cause the disappearance of the characteristic absorption bands of the individual pigment was taken as the reading for any particular fraction, and a curve was plotted from the values obtained. Values of urobilinogen and urobilin were added together, and the total taken as the pigment value of the fraction. An attempt was also made to quantitate the bilirubin values of the duodenal contents, by the method described by Hooper and Whipple in their work on dogs, but it was found impossible to obtain consistent readings on human bile owing to the conversion of bilirubin in some of the fractions into bilicyanin. The color obtained by this method, by treating the bile with acid alcohol, was in some instances the characteristic blue-green desired and could be read against a standard solution of copper sulphate as described by these authors. In the majority of cases, however, the color ranged from a decided green to a dark blue, and occasionally the entire series of fractions was intensely purple owing to the presence of bilicyanin. Similar observations on animals have been made recently by Rous and McMaster.[15] Bilirubin figures, when obtained, ran approximately parallel to those of urobilin and urobilinogen. The actual dilution figures obtained from spectroscopic examination were not multiplied by a constant, as done by Wilbur and Addis in their original work, and later by Schneider, as there seemed no advantage to be gained by this purely artificial procedure. The curves shown on the accompanying charts, therefore, represent actual dilution values of urobilinogen plus urobilin.

The method of fractional analysis, I believe, offers distinct advantages over the method of studying only a single specimen. It provides a free flow of bile into the duodenum over a considerable period of time, and permits the taking of an average figure as well as the value of individual fractions. In this way it is possible to make a comparative study of the different fractions, and to obtain a much more exact picture of the level of bile pigments than can be gained from any single observation. Even such a method, however, is open to error,

15. Rous and McMaster: J. Exper. M. **34**:47, 1921.

and I wish only to point out its advantages and to emphasize its relative accuracy.

In addition to an estimation of the bile pigment in the duodenal contents, Blankenhorn's [16] method for studying the bilirubin content of the blood plasma was employed. This method consists essentially in a comparison of the yellow color of oxalated plasma with distilled water. Dilutions of the plasma with water are made until the yellow color has disappeared. The number of dilutions necessary to remove the yellow color of the plasma are taken as the approximate bilirubin content of the specimen. Normally between fifteen and twenty dilutions give the desired end-point.

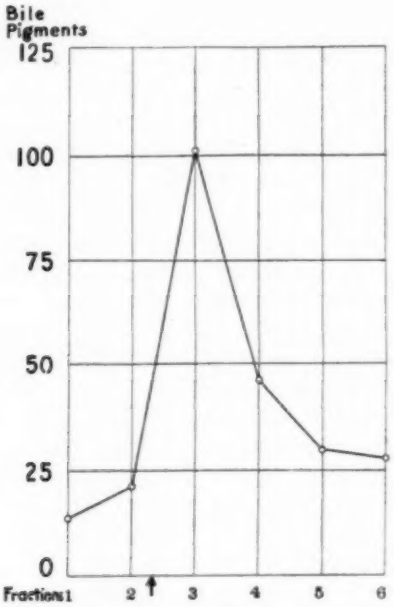

Chart 1.—Duodenal pigments in normal individuals. In this, and subsequent charts, points along the ordinates represent dilution values of the bile pigments, urobilin and urobilinogen. Points on the abscissae represent separate fractions of duodenal contents collected over fifteen minute intervals. The above curve is identical with the "normal" curves given in Charts 2, 3, 4 and 5, although in each case the scale varies. The arrow indicates the administration of 50 c.c. of a 33 per cent. solution of magnesium sulphate.

Bile Pigments in the Duodenal Contents in Normals.—As a basis for comparison with pathologic cases, observations on the pigment values in the duodenal contents of eight normal individuals were made

16. Blankenhorn, M. S.: Arch. Int. Med. **19**:344 (March) 1917.

and an average curve drawn from the results obtained. As shown in Chart 1, the average reading of all the six fractions in this series of normal cases was forty dilution units, with a maximum variation from this figure of ten units. The peak of the curve came shortly after the administration of magnesium sulphate and represents Lyon's "B" bile. The average pigment value of the peak of the curve was one hundred dilution units, with an individual variation up to fifty units. It will be seen that the variation from the average figures is a wide one, both in individual fractions and in the case of the general averages obtained from the total fractional estimations. These variations occurred in spite of the fact that duodenal contents in all cases were taken under similar conditions as regards the fasting state, the time at which the duodenal contents were collected and general freedom from symptoms. This point should be emphasized, inasmuch as previous investigators have inferred that the individual variation among normal persons is only a slight one. Furthermore, it is noticeable that there was a wide variation between individual fractions in the same normal person, even before the administration of magnesium sulphate. Bauer and Spiegel [10] have noticed similar variations in normal individuals in estimating the bilirubin content of the blood plasma. A further discrepancy may be observed between the pigment values in normals as given by Schneider and the values obtained before the use of magnesium sulphate in this series of determinations. My figures for normal individuals are relatively higher than those of Schneider. His average normal figure is about five dilution units. The results obtained from my series of normals, in the fractions that are comparable to his analyses, average about 8.5 dilution units. The difference between the two figures may be explained (1) by individual differences in obtaining end-points by spectroscopic examination, or (2) by the fact that specimens of duodenal contents were taken in this series after waiting a relatively long time following the introduction of the tube. Such a wait would insure a better flow of bile. In either event the differences are purely relative, and conclusions based on examinations of similar cases in both series are in the main identical.

In cases such as gastric ulcer, and so forth, in which there was no apparent cause for abnormal pigment values, there was essentially no deviation from the normal range.

Evidence of a Flow of Gallbladder Bile Following the Use of Magnesium Sulphate.—Following the establishment of the normal figures a series of cases was studied in which there was absolute obstruction of the cystic duct, as proved at operation, or in which the gallbladder had previously been removed. Obviously, there could be no flow of gallbladder or "B" bile in these cases and a comparison of results

obtained in these cases with the normal figures already given showed no characteristic peak after the administration of magnesium sulphate. On the other hand, there was only a moderate rise in pigment values after giving the salt, as shown in Chart 2. This rise can be explained entirely by a relaxation of the sphincter of Oddi, with a resulting free flow of undiluted bile into the duodenum.

In another series of cases in which there was definite gallbladder pathology without obstruction, the fractions taken immediately after the administration of magnesium sulphate, or in other words, those fractions taken at a time corresponding to the peak of the pigment curve, were the only ones to show certain cellular and crystalline ele-

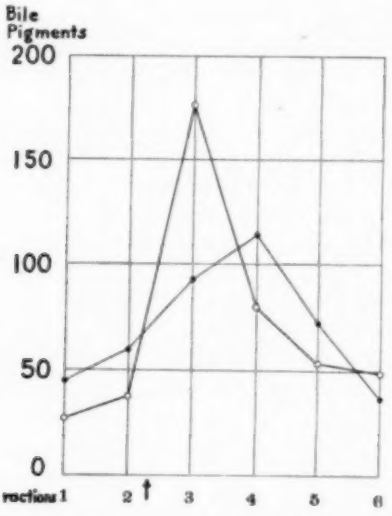

Chart 2.—Duodenal pigments in normal individuals as compared with pigments in patients with no flow of gallbladder bile. Normal pigment values o—o—o—o. Values with no gallbladder flow • — • — • — •

ments believed to be characteristic of gallbladder contents. The similarity of the sediments in these fractions to those actually obtained from the gallbladders at the time of operation was striking. The close correspondence between these sediment findings, their occurrence coincident with the peak of the pigment curves, and the absence of a characteristic pigment curve in cases where there was known to be no flow of bile from the gallbladders all confirm the assumption that the so-called "B" bile consists, at least in part, of actual gallbladder contents. The importance of this assumption will be discussed in a later portion of the paper in a study of cases in which there was known gallbladder pathology.

Relation of Blood Destruction to Bile Pigment Elimination.—It was desirable to establish, if possible, further definite evidence that there was a distinct relation between the amount of hemolysis going on in the body, and the level of the bile pigments. Observations were made in two cases of paroxysmal hemoglobinuria which have been reported in a separate paper.[17] In these cases immersion of the extremities in icewater caused immediate and marked intravascular hemolysis. The plasma, duodenal contents and urine were examined for changes in pigment values during the course of the observations, which covered a period of about twenty-two hours. There was no important change in urinary pigments inasmuch as the attacks produced were not severe enough to cause any but the slightest traces of hemoglobin to appear in the urine. The hemoglobinemia was immediate and intense and was accompanied in one case by a drop in the red count of over 800,000 cells per c.mm. Subsequently the hemoglobin content of the plasma rapidly diminished, with an accompanying marked increase in the bilirubin content. This increase in bile pigment in the plasma continued until it reached its height at a point coinciding with the disappearance of hemoglobin from the plasma. It then gradually dropped, reaching normal at the end of about eighteen hours. Coincident with the peak of the bilirubin content of the plasma, the duodenal pigments rose rapidly, reaching a level about six to eight times the normal level in about three hours. These pigments did not return to the normal level until after eighteen to twenty hours. These results rather definitely confirmed the generally accepted theory that increased blood destruction is accompanied by increased elimination of bile pigments. Furthermore, it seemed safe to assume from the above observations that the bulk of the hemoglobin liberated into the circulation as a result of any hemolytic process is rapidly taken care of within the liver and broken down into lower bile pigments. Although other organs and tissues possess a similar property of carrying on the metabolism of blood pigments, under normal conditions the liver probably carries on the greater part of this important chemical process.

Bile Pigments in Various Types of Anemia.—With the clear recognition that increased blood destruction is accompanied by an increased elimination of bile pigments in the plasma and bile, as demonstrated by the above observations on paroxysmal hemoglobinuria, and as brought out by numerous investigators, a series of cases of various types of anemia was studied. This series included cases of anemia due to severe hemorrhage, lowered bone-marrow activity, pernicious anemia, hemolytic jaundice, malaria, and so forth. A somewhat similar series had been studied by Schneider, and later by Giffin, Sanford and Szlapka.

17. Jones, C. M., and Jones, B. B.: Arch. Int. Med. **29**:669 (May) 1922.

I wished, however, to obtain a comparative set of figures by the fractional method of duodenal analysis, and to attempt a more detailed study of the abnormal physiology occurring in these diseases. The cases studied fell roughly into two groups: (1) cases in which increased blood destruction is believed not to be present, or at least is not an important feature, and (2) cases in which it is generally believed that abnormal blood destruction is an important feature of the disease process.

As examples of the first type of cases a group of patients was studied in which the anemia was due entirely to blood loss. The anemia was due in two cases to hemorrhage from duodenal ulcers, in one to renal hemorrhage, in one to a series of attacks of paroxysmal hemoglobinuria, and in one to prolonged menorrhagia. The case of paroxysmal hemoglobinuria had been free from attacks for more than a week, so that there was no complicating factor of recent hemolysis. In none of these cases was there any evidence of abnormal red cell destruction. As was to be expected, the actual pigment values were all under the normal average (Table 1), indicating possibly an attempt

TABLE 1.—Bile Pigments in Anemia from Blood Loss

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
20	28	35	12	65	4.0
21	7	12	11	32	2.6
22	36	72	10	28	2.5
23	21	30	9	80	3.7
24	13	20	18	50	3.2

on the part of the body to conserve hemoglobin. "Relative" figures, based on the actual pigment readings in the duodenal contents and the percentage of red cells in relation to normal, with one exception (Case 22), were also within or below the normal range. The single case referred to, with high "relative" figures, had a profound anemia, and the explanation for the high figures may lie in the fact that the liver was improperly functioning on account of the anemia itself.

"Relative" figures were obtained on the following assumption: The pigment values in the duodenal contents are in a sense absolute values, in that these values do not take into consideration the amount of circulating hemoglobin. Obviously, even if the pigment values in the duodenal contents are the same, there is greater relative blood destruction in a case with a low red count and hemoglobin than in a case with a normal red count and hemoglobin. It is interesting, therefore, to attempt roughly to correct these figures of pigment values to the same standard of circulating hemoglobin. Thus it is possible to ascertain the relative intensity of the blood destruction. It does not of

course necessarily follow that the same relative intensity of blood destruction would obtain if the red corpuscles and hemoglobin were at the normal level. Because it was simpler to carry out this correction on the basis of the numerical differences of red corpuscles, this procedure was adopted, rather than correction by utilization of hemoglobin variations, which theoretically is more logical. Relative figures were obtained by dividing the pigment values in the duodenal contents by the percentage of normal which the red count of the individual case showed, and then multiplying by 100. Thus, for example, a patient with a count of 3,000,000 red corpuscles per c.mm., and a pigment average of 100 units, other things being equal, would theoretically be destroying one-half the percentage of total red cells destroyed by a patient with a count of 1,500,000 red corpuscles per c.mm., and a pigment average also of 100 dilution units.

TABLE 2.—BILE PIGMENTS IN A CASE OF APLASTIC ANEMIA

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
25	28	108	11	26	1.3

A single case of true aplastic anemia (Table 2) was studied, which also showed actual bile pigment values well below the normal. However, the "relative" figures were high. Inasmuch as in this case also the anemia was extreme, the explanation of the high "relative" figures is possibly the same as that given for Case 22 of the preceding series, namely, the effect on liver function of the profound anemia. A more logical explanation may possibly be that, with an extremely low level of red corpuscles, and with practically no new blood formation, the few cells in the circulation undergo more rapid dissolution than normal on account of the undue work put on them.

TABLE 3.—BILE PIGMENTS IN A CASE OF POLYCYTHEMIA VERA

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
38	54	22	24	155	8.0

One case of polycythemia vera was studied. The patient had a red cell count of 8,000,000 cells per c.mm., and a hemoglobin content of 155 per cent. The actual pigment values averaged only slightly above normal (Table 3), but the "relative" figures were below the normal average. In spite of the enormous increase in the number of red cor-

puscles the process of blood destruction in this case was apparently normal, or even relatively below normal.

In contrast to the above cases, and as an instance of disease in which it is generally conceded that there exists an apparently high degree of blood destruction, a series of nineteen cases of pernicious anemia was studied. Other observers have pointed out that in pernicious anemia there is a marked increase in the bile pigments in the blood, duodenal contents, stools and urine.

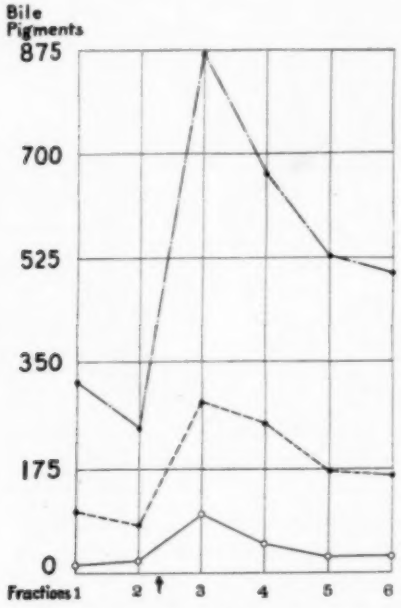

Chart 3.—Duodenal pigments in pernicious anemia. "Relative" pigment values —·—·—·—·—. Actual pigment values - - - - - - - -. Normal pigment values o-o-o-o-o-o.

Observations made in this series of cases entirely confirmed the results of previous investigators. There was a high level of bile pigments both in the blood plasma and in the duodenal contents. The average increase in duodenal pigments over normal was more than 500 per cent.; the highest averages were nine times, and the lowest twice the normal figures. Plasma bilirubin was, in the average, about four times normal; the highest figure was about eight times the normal, while the lowest was about twice normal. Based on average figures, therefore, the bile pigment content of the blood and duodenal contents ran about parallel, but in individual cases there was marked discrep-

ancy between the two values. This difference, in individual cases, between the pigment content of the plasma and the pigment values of the duodenal contents, is perhaps significant, and suggests some interference with liver function—a point that will be discussed later.

A question of considerable interest to be determined in studying these cases was whether the level of bile pigments in the duodenal contents corresponded with the actual clinical condition of the patients. Weakness, elevation of temperature, icterus, level of hemoglobin and red cells, etc., supply the clinician with evidence for comparison between individual patients. The condition of the individual patient theoretically depends, in large measure, on the relative severity of the hemolytic process and on the relative degree of blood-forming activity. Thus, a patient who is subjectively sick, and who presents the typical features of a relapse, usually gives evidence of a marked predominance of blood destruction over blood formation. A patient, one the other hand, with few subjective symptoms, a high hemoglobin content, usually shows evidence of little blood destruction and, on the contrary, a satisfactory blood formation. In spite of the theory that varying degrees of blood destruction are accompanied by corresponding variations in the level of the bile pigments, it is evident that changes in blood formation may modify the clinical picture to such an extent that the level of the bile pigments in the duodenal contents, although measuring the amount of blood destruction taking place, will not reflect the patient's clinical condition. High pigment values might, therefore, be obtained, even in the presence of a severe degree of blood destruction, without correspondingly severe clinical symptoms. Furthermore, any alteration of liver activity should modify the bile pigment excretion, both in the bile and in the blood plasma.

These theoretical considerations were well sustained by the findings. Examination of the figures obtained in the nineteen cases of pernicious anemia showed that the actual pigment values corresponded only in a very rough way to the clinical condition of the patient. Patients whose duodenal pigments were very high frequently were clinically less sick than those who showed relatively low bile pigment estimations, and vice versa. A second set of figures, however, did correspond closely to the condition of the individual patient, both as regarded his clinical condition and as concerned the actual physiologic processes taking place. These second figures are the "relative" figures already referred to, and were obtained by dividing the actual pigment readings by the percentage of red cells of the particular case. Such a modification of the actual pigment readings gave a close approximation to the clinical state of the patient, and in addition appeared to serve as a much clearer index of the relation of blood destruction to blood formation. Actually,

patients with high "relative" figures were sick, and presented the clinical findings of severe blood destruction—elevation of temperature, jaundice, etc., that are typical of a severe relapse. Those patients whose "relative" figures were only moderately high, on the contrary, were free from the more marked symptoms, while patients with "relative" pigment values at a still lower level were in a well marked remission. The average level of the "relative" figures, however, was about three times that of the actual readings, and indicates clearly the severity of the disease process. Furthermore, a comparison of the actual and "relative" values in any individual case provided a fair estimate of the balance between blood destruction and blood formation. When the two sets of figures were not far apart it would appear that the two processes were taking place at about equal rates; when the "relative"

TABLE 4.—Bile Pigments in Nineteen Cases of Pernicious Anemia

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
1	185	1,543	96	25	0.6
2	331	1,370	36	42	1.6
3	272	1,200	56	40	1.0
4	200	858	64	37	1.2
5	102	845	40	31	1.2
6	233	832	160	46	1.4
7	193	801	32	35	1.2
8	141	748	90	27	0.9
9	165	717	64	35	1.2
10	99	596	90	27	0.8
11	194	571	30	50	1.7
12	164	512	90	55	1.7
13	200	500	100	94	3.5
14	357	496	32	75	3.6
15	175	333	65	45	2.7
16	133	302	30	70	2.2
17	132	300	50	55	2.2
18	117	278	32	60	2.1
19	68	112	80	85	3.7
Average	194	682	66	48	1.8

figure was much higher than the actual reading it would seem that blood destruction was exceedingly active, and vice versa. Table 4 illustrates these points. The actual readings in the first column and the "relative" figures in the second column are both obtained by averaging the total pigment values of the six fractions obtained during duodenal drainage. The cases are arranged in order of magnitude of the "relative" figures and, as noted above, this order closely approximated the severity of the patient's clinical condition. Case 1, for example, was a patient in a very severe relapse, while Case 19 was a patient in a well marked remission with almost complete freedom from symptoms. Chart 3 illustrates the marked increase in big pigment elimination in these cases over the normal level, and further emphasizes the difference between the actual and "relative" findings.

Mention has already been made that in these cases of pernicious anemia the bile pigment in the plasma did not always exactly parallel the pigment content in the bile, although it was always well above normal, as previously shown by Blankenhorn. Such a finding suggests that this failure of the plasma bilirubin to parallel the bile pigments in the duodenal contents may be due to an alteration in hepatic function. It is pertinent, at this point, to call attention to a question only briefly noted in the literature. The average level of bile pigments in the duodenal contents in this series of cases of pernicious anemia is by actual reading 194 dilution units, or about five times the normal values.

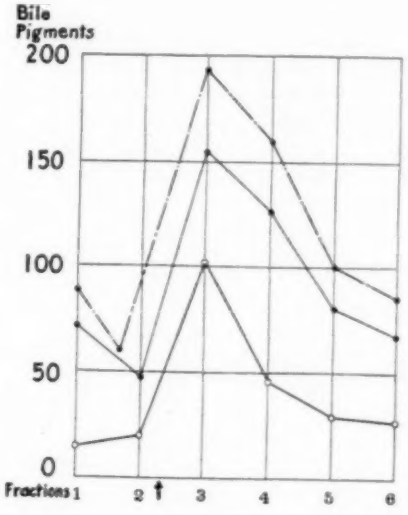

Chart 4.—Duodenal pigments in liver disease. "Relative" pigment values —·—·—·—·—. Actual pigment values ————. Normal pigment values o-o-o-o-o-o.

Individual cases went as high as eight to nine times the normal level. Such an increase over normal has previously been considered as due entirely to increased blood destruction, with excessive liberation of hemoglobin. Undoubtedly some part of the excess of bile pigments is due to the products of increased red cell destruction, but there is in addition a second factor which must be taken into account. Comparison with the observations on paroxysmal hemoglobinuria already mentioned makes this clear. One of the artificially produced attacks of hemoglobinemia was accompanied by a lowering of the red cell count by as much as 850,000 cells per c.mm. The hemoglobin liberated into the circulation was presumably derived solely from the destruction of

red cells, a destruction which approximated more than one-tenth of the total number of red cells, as measured by a routine red count. This excessive destruction of blood was followed shortly afterward by a rise in the bile pigments in the duodenum to a level of about 300 dilution units, or between six and eight times the normal figures. In paroxysmal hemoglobinuria there is no known evidence of any liver injury. Deranged liver function, therefore, need not be considered in paroxysmal hemoglobinuria, and any increase in bile pigments can safely be attributed essentially to increased blood destruction. In this example of pure hemolysis, uncomplicated by any other factors, a drop in the red cell count of 850,000 was accompanied by a rise in duodenal pigments to a level of about 300 dilution units. This level of bile pigments was well above the average of the entire series, and was but little under the level found in the most severe cases of pernicious anemia. It is difficult to conceive, even in the most severe cases of pernicious anemia, or in any other so-called hemolytic disease, that there is a constant rate

TABLE 5.—Bile Pigments in Other "Hemolytic" Diseases

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
Malaria:					
27	95	130	25	45	3.9
28	182	284	128	38	3.2
Hemolytic jaundice:					
29	228	251	120	70	4.6
30	139	430	100	30	1.5
31	132	625	65	40	1.2
32	108	99	45	70	5.5

of blood destruction going on so rapidly as to cause in a few minutes the dissolution of more than one-tenth of the total blood corpuscles in the body. A process causing such a degree of blood destruction, in the absence of a correspondingly rapid degree of blood formation, ought to result in complete exsanguination in a very short space of time. A second factor seems necessary to help explain the high level of bile pigments found in pernicious anemia. Ashby [18] has recently reached a somewhat similar conclusion. This second factor, I believe, lies in a marked impairment of liver function. Such an assumption, although suggested by Hooper and Whipple as a result of their work on dogs, has not been made as a result of observations in man.

In addition to the above cases of pernicious anemia, a number of cases were studied in which it is also usually agreed that there exists an abnormally high degree of blood destruction. This series contained two cases of malaria and four cases of acquired hemolytic jaundice. One of the latter had previously had his spleen removed. All of these

18. Ashby, W.: J. Exper. M. **34**:147, 1921.

cases showed high pigment values (Table 5) entirely comparable with those observed in pernicious anemia. As in the former cases, the "relative" figures gave the more accurate picture, and closely paralleled the clinical condition of the patients. In these cases, also, as in pernicious anemia, it seems reasonable to assume that there must be a second factor to account for the extremely high bile pigment values obtained. Blood destruction alone could hardly account for the increased bile pigment elimination. In two of the cases of acquired hemolytic jaundice in this series (Table 5, Cases 30 and 31) the liver enlargement was so marked indeed as to dominate the entire clinical

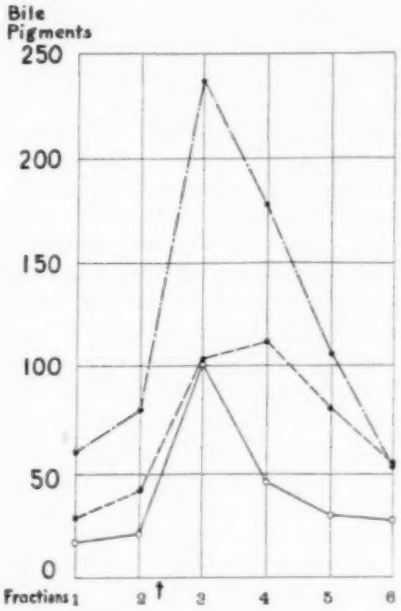

Chart 5.—Duodenal pigments in gallbladder disease. Pigment values in cholecystitis —·—·—·—. Pigment values in cholelithiasis - - - - - - -. Normal pigment values o-o-o-o-o-o-o.

picture and to suggest definitely that a hemolytic process was not responsible for the entire condition. Impairment of liver function in these cases would also seem to be the logical additional factor to be considered, and such an assumption would seem to be even more logical in the cases of hemolytic jaundice than in the cases of pernicious anemia.

Bile Pigments and Impaired Liver Function.—In the type of cases already studied, in which the process of abnormal blood destruction

has been of long duration, it is well recognized that clinically, and at post-mortem examination, it is commonly possible to demonstrate liver pathology. Forty per cent of cases of pernicious anemia have during life palpable livers,[19] which at autopsy show a certain amount of fatty infiltration and deposits of iron containing pigment. Cases of hemolytic jaundice usually, and malaria not infrequently, present the clinical evidence of liver enlargement. The suggestion has already been made that in the above type of disease the abnormally high elimination of bile pigments may be due in part to an alteration of liver function. It is furthermore reasonable to assume, even in the absence of any clinical signs of liver derangement, that there exists a marked alteration in liver function, due merely to the presence of a severe anemia. Such an assumption finds support in the well-recognized fact that in cases of severe anemia the kidneys may show evidence of definite alteration of function by renal function tests and by the presence of albumin in the urine. With improvement in the anemia, the renal function also improves. It is, therefore, appropriate to turn from a consideration of the so-called hemolytic diseases, in which abnormal blood destruction and liver damage may be accompanying factors, to the study of a series of cases in which it is evident that the liver is the primary seat of disease, and in which there is considered to be little or no question of abnormal hemolysis.

A series of eighteen cases was examined, all of which presented clinical evidence of moderate to severe liver damage. This group included cases of carcinoma of the liver, cirrhosis, either alcoholic or syphilitic, hepatitis or cirrhosis due to a local or general infectious process, and Banti's disease. These types of cases are not usually considered to have any important degree of increased blood destruction, with the possible exception of Banti's disease. These cases, therefore, were of interest as a basis for studying the functional capacity of the liver, in terms of hemoglobin and bile pigment metabolism. The findings are tabulated and shown in Table 6 and Chart 4.

Six of the eighteen patients were clinically jaundiced, and nine more showed a "potential" jaundice. By the term "potential" jaundice is meant a condition in which the bilirubin content of the blood plasma is abnormally high but not sufficiently high to cause tissue icterus. As has been shown by Blankenhorn,[16] in certain chronic diseases in which there is a continual abnormal elimination of bilirubin, the concentration of this pigment in the blood plasma may be many times normal without causing tissue icterus. In spite of the presence of jaundice, either actual or "potential," in fifteen out of these eighteen cases the output of bile pigments into the duodenum was above normal. In the

19. Minot, G. R.: Oxford Medicine, **2**:623.

remaining three cases, the concentration of the bile pigments in the bile was within normal limits. Although some clinical abnormality in the liver was demonstrable, the abnormality may not have progressed far enough to overstep the large factor of safety present in this organ.

In fifteen out of eighteen cases, therefore, the liver, even when almost entirely invaded by foreign tissue, tended not to eliminate a decreased amount of bile pigment into the duodenum, but on the contrary to put out highly concentrated bile, as measured by pigment content. The actual pigment readings in the series of eighteen cases of liver disease showed an average curve (Chart 4), the values of which were over twice the normal level. From these facts alone, therefore, it is evident that the jaundice present in these cases was not at all obstructive in nature, at least in the usual interpretation, namely a diminished output of bile into the duodenum with accumulation of the residue in the blood and tissues.

Neither was the jaundice strictly hematogenous. The abnormal elimination of bile pigments, both in the bile and plasma, can not be said to be due to an increased amount of blood destruction. The average red cell count of the entire series was 3,900,000 corpuscles per c.mm., and one of the more severe of the cases, one of advanced carcinoma of the liver, showed a red count as high as 6,000,000 per c.mm. The red cells were markedly achromic, and the average hemoglobin content of the blood was approximately 60 per cent. The average color index of the cases was only 0.75, in contrast to the average index of 1.5 observed in the cases of pernicious anemia. In the stained smear the red cells showed only achromia, with slight variations in size and shape. There was lacking microscopic evidence of increased blood destruction; namely, the presence of microcytes or fragmentation of the red cells. Active blood formation, commonly present in the face of active blood destruction, was not seen, at least as represented by noteworthy changes in the number of young red cells. The usual conception of these types of liver disturbance, furthermore, does not associate them with increased blood destruction. Banti's disease, by some clinicians, is occasionally associated with abnormal destruction of the red corpuscles. The commonly accepted view, however, is that expressed by Krumbhaar,[20] who states that blood destruction is not the important element in this disease. It seems fair to assume, therefore, from the generally accepted views, that in these cases under discussion blood destruction was not importantly increased, and that the jaundice is not hematogenous in nature.

In the literature scant reference has been made to the bile pigment excretion in the above type of case. The general statement has usually

20. Krumbhaar, E. B.: Nelson's Loose Leaf Living Medicine, **4**:37.

been made that secondary anemias, in contrast to primary anemias, are accompanied by a diminished elimination of bile pigments. It is clearly evident, however, from the results charted in Table 6, that cases of anemia associated with liver disturbance are usually accompanied by increased bile pigment excretion. The so-called secondary anemias, if uncomplicated by liver disturbance, undoubtedly yield low pigment readings. When, however, in the course of such a secondary anemia the underlying cause affects the liver the entire picture of bile pigment excretion is changed, and instead of a low pigment elimination in the bile and plasma, there follows a complete reversion of the physiological processes involved, and the bile pigments reach a new and abnormally high level.

TABLE 6.—BILE PIGMENTS IN CASES OF LIVER DISEASE

Case	Average Bile Pigments in Duodenal Contents	"Relative" Duodenal Pigments	Plasma Bilirubin Content	Hemoglobin, per Cent.	Red Blood Cells (Millions)
Cancer:					
50	173	144	40	85	6.0
51	144	200	80	62	2.6
52	98	213	15	25	2.3
53	57	54	40	80	5.3
Cirrhosis (alcoholic):					
54*	151	189	30	65	4.0
55	64	60	30	80	5.3
56	36	...	50	75	
Cirrhosis (syphilitic):					
57*	77	96	140	68	3.9
58	41	51	66	40	1.2
Hepatitis (infectious):					
60	98	...	28	75	
61	115	174	25	45	3.3
62*	78	87	100	70	4.5
63 (typhoid)	81	96	10	..	4.2
64	30	35	15	65	4.3
65*	30	35	250	67	4.2
70*	248	248	72	72	4.8
Hepatitis (toxic):					
66	58	55	30	80	5.3
Banti's disease:					
67*	230	280	150	65	4.1
Average	101	114	59	66	4.1

* Clinically jaundiced.

It has already been shown that the jaundice occurring in such cases is neither strictly obstructive nor hematogenous in nature, in spite of the fact that in all the cases the liver parenchyma was severely damaged. It is well known that the liver, like the other organs, has a large factor of safety, as regards all of its functions. Exact information as to the extent of this measure of safety has never been determined in man. McMaster and Rous [21] have recently shown that the bile ducts from three-quarters of the liver substance can be obstructed in dogs and monkeys without the development of any clinical evidence of pigment or cholate accumulation in the organism. They also

21. McMaster and Rous: J. Exper. M. **33**:731, 1921.

showed that in the dog nineteen-twentieths of the liver substance can be placed in a condition of stasis, without the occurrence of tissue icterus such as regularly follows total obstruction in this animal. In their experiments, they found that invariably a local obstruction resulted sooner or later in atrophy of the affected tissue, with compensatory hypertrophy elsewhere. Their conclusions are of particular interest in the present discussion: "the clinical jaundice encountered in association with local liver lesions should be viewed, not as the result of local bile absorption, but as due to a general injury to the hepatic parenchyma or ducts, or to blood destruction." Such injury with its resulting hypertrophy, would accordingly result in functional changes, and bile pigment excretion would accordingly be modified. The nature of the cause of this functional disturbance is apparently not specific. An examination of the accompanying table will show that in no particular group of liver conditions was there any predominance of high pigment values. Bile pigment excretion was apparently influenced neither by the nature of the process, nor by the amount of the anemia. The mechanism is probably similar in all the cases, and the degree of derangement of hepatic function is solely dependent on the extent and rapidity of the disease process.

There remains, then, to discuss the actual nature of this alteration in liver function. As already noted, there was a marked increase in the actual amount of bile pigments eliminated by the liver. In the absence of any abnormal process of blood destruction the source of the excessive amounts of bile pigments is still to be determined. Changes in diet, according to Hooper and Whipple,[9] can cause marked alterations in bile pigment elimination in animals. Such a factor, however, can readily be excluded in the present series. The most logical explanation seems to be the following: Under normal conditions the liver is the principal agent in the metabolism of hemoglobin set free during the normal processes of red cell destruction. This pigment metabolism involves the breakdown into less complex molecules, through bilirubin and biliverdin, to the lower derivatives, urobilinogen and urobilin. The formation of bilirubin from hemoglobin may take place in the blood vessels and tissues without any intervention on the part of the liver, and similarly, urobilin is undoubtedly formed in the intestine by the action of bacteria on bilirubin. It is highly probable, however, that the liver itself is capable of breaking down the bilirubin into urobilin, without the intervention of the intestine. The observations already mentioned made on cases of paroxysmal hemoglobinuria suggest such a possibility. Furthermore, the liver has long been thought capable of resynthesizing hemoglobin from the lower bile pigments by building them up to more complex molecules and combining them with the iron

known to be retained by the liver. Such a process of resynthesis is entirely analagous to the general physiologic properties of all human cells and is not necessarily much more complicated than the formation of urea or glycogen from lower chemical constituents. The process of breaking down hemoglobin into its lower derivatives is, however, probably a less difficult matter than the subsequent resynthesis of hemoglobin from bile pigments. The latter function would perhaps logically be the first to be altered or lost. With the failure of the normal resynthesis of hemoglobin from bile pigments the unaltered bile pigments would then form an excess and would be eliminated as such in the bile.

The findings in this group of cases seem to confirm this supposition. The loss of resynthesizing power in a damaged liver would, of course, be only partial. The lowered formation of hemoglobin ought eventually to be reflected in a diminished hemoglobin content of the red cells with resulting low color index and achromia. In all these cases marked achromia of the red cells and a low color index occurred. The hemoglobin averaged 66 per cent., and the red count averaged 4,100,000 per c.mm. This slight diminution was possibly the result of a gradual slowing up of bone marrow activity. Such findings may be regarded as probable evidence of a diminished production of hemoglobin. That portion of the bile pigments not resynthesized into hemoglobin would be excreted as such, and would account for the increased elimination of bile pigments, even in the face of normal blood destruction. That such a theory further corresponds with the actual findings in the individual cases is attested by the fact that in the majority of cases showing the greatest reduction of hemoglobin content there was a proportionally high level of bile pigments in the duodenum. One case, for example, with a hemoglobin content of 40 per cent. and a color index of 0.35, showed a bile pigment elimination in the bile of over four times the normal.

The above theory would satisfactorily account for the appearance of jaundice and lowered hemoglobin content so frequently noticed in the course of acute infections such as pneumonia, typhoid, scarlet fever, septicemias, etc. In such conditions the infection, or the accompaning toxemia, may be assumed to cause a temporary alteration of the liver function, with resulting alterations in hemoglobin metabolism. The icterus frequently accompanying severely decompensated heart disease may also be explained on the basis of altered liver function.

In a severely damaged liver not only should there be an increase in the actual amount of bile pigments eliminated, but the relation of the various pigment elements in the bile should be distinctly altered. Those pigments most easily formed ought to be excreted at once instead of

being completely broken down to the lower forms. In confirmation is the frequent occurrence of excessive amounts of intermediate bile pigments—cholecyanin and urobilinogen—found in the duodenal contents in this series of cases of excessive red cell destruction, and those with liver disease. Schneider and others have already noted the presence of large amounts of urobilinogen in the duodenal contents in severe cases of blood destruction. This excess of urobilinogen was noted, not only in the present series of cases with liver disease, but also in those cases in which there was pathologic blood destruction. In addition, in those cases of severe anemia, the presence of cholecyanin was observed, frequently in large amounts. This latter pigment, as well as urobilinogen, is intermediate between bilirubin and urobilin, and its presence would seem to indicate very rapid and incomplete metabolism of hemoglobin derivatives by the liver. The presence, therefore, of these intermediate pigments in excess in cases of pernicious anemia would seem further evidence of liver damage in this disease.

It is therefore, tempting to assume that a disturbed function of the liver in the disease pernicious anemia is a considerable factor in creating abnormal pigment values in the plasma and in the bile. It is not as easy, however, to apply this explanation to pernicious anemia as to the other anemias in which abnormal pigment values are found. In pernicious anemia there is a relative increase in hemoglobin and iron pigment is found in various organs. The irregular and biazarre course of pernicious anemia, the attractive assumption that the red corpuscles in pernicious anemia are not only abnormal but different from the red corpuscles in other conditions, may account in part for the seeming discrepancy. The existence of difference between the red corpuscles in pernicious anemia and in other conditions has been indicated by work recently done on various types of anemia by Buckman [22] at the Boston City Hospital. In any event, while a part of the increase in bile pigment elimination in pernicious anemia may be attributed to excessive blood destruction, the remainder may perhaps be laid to a damaged liver. Inasmuch as continued attacks of hemolysis per se cause liver damage, the two factors are really related.

Furthermore, as pointed out by Brulé,[23] the proper conception of such a disease as catarrhal jaundice should locate the primary pathology not in the biliary passages but in the hepatic cell itself. Such a disease is primarily an infection of the liver parenchyma, and the pathology and abnormal physiology should be centered in the degree of actual parenchymal damage and disturbance of liver function. Such a conception of catarrhal jaundice offers the logical explanation of the

22. Buckman, T. E.: Personal communication.
23. Brulé, M.: Bull. méd. **8**:279, 1920.

diminished hemoglobin frequently found after an attack of even moderate severity, and accounts for the increased amounts of bile pigment eliminated in the bile after the flow is reestablished.

Findings in Cases of Gallbladder Disease.—In view of the frequent association of liver disturbance with chronic disease of the gallbladder it is pertinent at this point to examine briefly the results obtained in a series of cases of cholelithiasis and cholecystitis. Observations were made on ten patients suffering from typical gallstone attacks and on six patients with typical symptoms of chronic cholecystitis. In a majority of the cases the preliminary diagnosis was confirmed by subsequent operation. The pigment curves, as shown in Chart 5, are easily explained. They did not vary from the normal curve in their general contour. The actual level of the bile pigments, however, was distinctly higher than normal. (This series, of course, did not include cases of cystic or common duct obstruction.) The point of interest in these cases is that there was a distinct difference between the pigment values obtained from patients with stones and those obtained from patients with only cholecystitis. Those patients with cholelithiasis gave an average pigment curve approximately 75 per cent. above the normal level, although in individual cases the average figure was as high as three times normal. The cases of cholecystitis, on the contrary, gave a distinctly higher average. The average pigment values in this group were nearly twice those observed in cases with stone formation, and and were three times the normal figure. Individual cases of this group went as high as eight times normal. Furthermore, the peak of the pigment cure representing the greatest concentration of gallbladder bile was on the average more than twice that found in the group of cases with stones. According to the present conception of gallbladder disease, blood destruction does not play an important part in the disease process. The high pigment values, therefore, were due either to abnormal stasis or to liver pathology. The work of Rous and of McMaster,[24] recently published, indicates that in stasis the gallbladder has a great power of concentration, with the result that any bile contained in it, even for short periods of time, becomes abnormally high in pigment and other constituents. They show that this power of concentration diminishes in the face of a pathological process such as the presence of stone formation with partial or complete obstruction to the normal entrance of bile into the gallbladder. The high pigment content in cases of cholecystitis may thus be partially explained as well as the difference between those cases with stone formation and those with only low grade gallbladder inflammation leading merely to stasis. It is of especial interest in this consideration to note the findings reported

24. Rous and McMaster: J. Exper. M. **34**:47, 75, 1921.

in a personal communication from Fitz [25] from the Mayo Clinic. He reports finding highly pigmented bile in most cases in which operation was performed for cholecystitis, whereas the bile in those cases showing calculus formation was also dark but less highly pigmented. Furthermore, he was able to demonstrate that the specific gravity and the nitrogenous content of those cases with only cholecystitis tended to be much higher than in cases of cholelithiasis. Such findings are strongly confirmatory of the concentrating ability of the gallbladder in cholecystitis and help to explain the pigment values found in this group of cases.

While the high pigment values in these cases are undoubtedly due in part to gallbladder concentration, it is also highly probable that they may be due in part to an accompanying cholangeitis and hepatitis. The recent paper by Judd,[26] emphasizing the common association of gallbladder and liver infection, is also confirmatory. Such a conception would also explain the low hemoglobin content frequently found in connection with long standing cases of cholecystitis, and occasionally persisting even after cholecystectomy. The high pigment values in such cases are probably due both to abnormal gallbladder concentration and to an alteration in liver function.

CONCLUSIONS

1. Increased blood destruction is accompanied by an increase of the bile pigments in the blood plasma and bile.

2. Alterations in liver function, due to infection, new growth, cirrhosis, or even a profound anemia per se, are also accompanied by marked increases in bile pigment, both in the bile and plasma.

3. Jaundice, in cases with liver damage, may be entirely due to an alteration in bile pigment metabolism, without the necessity of any accompanying obstructive process or increase in the normal process of blood destruction.

4. The high level of the bile pigment in pernicious anemia can not be due solely to a process of increased blood destruction. A second factor is necessary to explain the increased pigment elimination. This second factor may well be an alteration in hepatic function.

5. In gallbladder disease the bile pigments in the duodenal contents are abnormally high, especially in those fractions containing the greatest concentration of bile from the gallbladder.

6. Cases of uncomplicated cholecystitis show a greater concentration of bile pigments than cases of cholelithiasis.

25. Fitz, R.: Personal communication.
26. Judd, E. S.: J. A. M. A. **77**:197 (July 16) 1921.

7. A presumable functional incapacity of the liver properly to metabolize hemoglobin, due to any cause resulting in liver damage, is accompanied by a lowered hemoglobin content of the blood. Such cases also show high bile pigment values in the plasma and bile.

8. Owing to the frequent association of hepatitis with cholecystitis it is probable that the frequent accompaniment of a low hemoglobin content and an apparent anemia in chronic gallbladder diseases is due to an alteration in liver function.

For numerous valuable suggestions and criticisms offered during the course of this work I am greatly indebted to Dr. Roger I. Lee and Dr. George R. Minot. I also wish to acknowledge the cooperation of Dr. Thomas E. Buckman in allowing me access to the clinical material of the Boston City Hospital.

A STUDY OF HEMOGLOBIN METABOLISM IN PAROXYSMAL HEMOGLOBINURIA

WITH OBSERVATIONS ON THE EXTRAHEPATIC FORMATION OF BILE PIGMENTS IN MAN *

CHESTER M. JONES, M.D.
AND
BASIL B. JONES, M.D.
BOSTON

The close relationship of the coloring matter of the red blood corpuscles to the pigments of the bile is now generally accepted. Proofs for the existence of this relationship are numerous, and have been obtained by many investigators. Hematoidin, chemically isomeric with bilirubin, has long been known to occur in old extravasations of blood. Stadelmann,[1] working on dogs with biliary fistulas, showed that free hemoglobin in the plasma, produced by the artificial destruction of red cells, or by the injection of hemoglobin into the circulation, caused an increase in the quantity of bilirubin in the bile. Stadelmann and Gorodecki,[2] by injecting a solution of hemoglobin either subcutaneously or intraperitoneally, also caused in dogs a marked and prolonged rise in bile pigment in the fistula bile. The work of Brusch and Yoshimoto,[3] on dogs with biliary fistulas and ligated bile ducts, showed that intravenous injections of hematin caused increased amounts of bilirubin and urobilin to appear in the bile. In man the excretion of bile pigments in various so-called hemolytic conditions has been studied by numerous investigators. These conditions are found in pernicious anemia, hemolytic jaundice, malaria, etc. Hoppe-Seyler,[4] Gerhardt and von Müller,[5] Eppinger and Charnas,[6] de Jonge,[7] Simpson,[8] Robertson,[9]

* From the Medical Service of the Massachusetts General Hospital.

* This paper is No. 23 of a series of articles on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed from a grant from the Proctor Fund of the Harvard Medical School for the study of chronic disease.

1. Stadelmann: Der Icterus und seine verschiedene Formen. Stuttgart, 1891.
2. Stadelmann and Gorodecki: Ibid.
3. Brusch and Yoshimoto: Ztschr. f. exper. Path. u. Therap. **8**:639, 1910.
4. Hoppe-Seyler: Virchows Arch. f. path. Anat. **30**:124, 1891.
5. Gerhardt and von Müller: Ztschr. f. klin. Med. **32**:303, 1897.
6. Eppinger and Charnas: Arch. f. klin. Med. **78**:387, 1913.
7. de Jonge: Geneesk. Tijdschr. v. Nederl. Ind. **44**:435, 1904.
8. Simpson, G. C. E.: Biochem. J. **5**:378, 1911.
9. Robertson, O.: Arch. Int. Med. **15**:1072 (June) 1915.

Wilbur and Addis,[10] and others have investigated the urine and feces for urobilin in human beings in normal and diseased conditions. In cases in which there was apparently a rapid rate of blood destruction these observers consistently noted abnormally large amounts of urobilin in the feces, and usually in the urine. Simpson reported one case of malaria which showed hematoporphyrin, as well as large amounts of urobilin in the stool examinations. Schneider,[11] Giffin, Sanford and Szlapka,[12] and Jones [13] and subsequent workers have demonstrated abnormally large amounts of bilirubin, urobilin and urobilinogen in the duodenal contents, particularly in cases of pernicious anemia, and other conditions in which blood destruction is considered to be excessive. The bilirubin content of the blood plasma has been shown by Blankenhorn,[14] among others, to be definitely increased in diseases in which it is usually considered that pathologic blood destruction is taking place.

From the literature it is clear that a large amount of evidence has been obtained as proof of the close relationship between liberated hemoglobin and the bile pigments in the blood, bile and excreta. It is true, however, that the relationship between the amount of hemoglobin liberated during the process of blood destruction at any given time and the bile pigments in the blood and bile, as measured by present laboratory methods, may not be strictly a quantitative one. On the contrary, although the level of bile pigments in the blood and bile undoubtedly may serve as an index or measure of blood destruction, it is, nevertheless, only a relative measure of hemolysis, and may be influenced by various factors. Hooper and Whipple,[15] have shown in dogs, that mere changes in diet can produce large variations in bile pigment excretion. In dogs with biliary fistulas, a high carbohydrate intake resulted, and in some cases an increase in fistula bilirubin as high as 100 per cent. above normal, while a meat diet alone gave a slight decrease in pigment values. These observers also showed that the functional capacity of the liver, in dogs, in large measure influenced the output of bile pigments. Dogs with Eck fistulas, and accordingly with damaged livers, showed a marked diminution in bile pigment elimination. On the contrary, Jones [13] was able to demonstrate, in a series of patients suffering from various types of liver disease, a marked increase in the output of the bile pigments, both in the blood and the bile. The use of certain drugs is also known to modify bile pigment excretion.

10. Wilbur and Addis: Arch. Int. Med. **13**:325 (March) 1914.
11. Schneider, J. P.: Arch. Int. Med. **17**:32 (Jan.) 1916.
12. Giffin, Sanford, and Szlapka: Am. J. M. Sc. **182**:562, 1918.
13. Jones, C. M.: This issue, p. 643.
14. Blankenhorn, M. A.: Arch. Int. Med. **19**:344 (March) 1917.
15. Hooper and Whipple: Am. J. Physiol. **40**:332, 349, 1916.

It has also been shown by recent investigators that the early views regarding the mechanism of hemoglobin metabolism must be modified considerably. The liver, and to some extent the spleen, were originally held to be the sole agents concerned with the breakdown of hemoglobin. The liver alone was held responsible for the reconstruction of hemoglobin from iron and the lower pigment molecules. Recent work, however, has shown that, whereas the liver undoubtedly plays the most important rôle in hemoglobin metabolism under normal conditions, this function, in animals, can be assumed, in part, if not entirely, by other organs and tissues of the body. Hooper and Whipple [15] were able to show in dogs with bile fistulas that the bile pigments could be formed just as readily in animals in which the circulation of the liver was greatly diminished by an Eck fistula, or with such a fistula and the hepatic artery ligated, as in normal animals. Injection of hemolyzed red blood corpuscles into a head-thorax circulation resulted in the appearance of increased bile pigments in the blood. Bile pigments were also found in increased amounts in the blood when free hemoglobin was injected into the pleural or abdominal cavities. Van de Bergh [16] has also shown in man, in four cases subjected to operation, and in two necropsies, that the blood serum from the splenic vein contained much more bilirubin than did the peripheral blood. These patients had pernicious anemia, Banti's disease, hemolytic jaundice, etc. He concludes that the excess bilirubin in the splenic blood was formed by the spleen. The views recently expressed by Pearce, Krumbhaar and Frazier,[17] that the spleen is an important factor in the process of blood destruction, are very generally accepted. In fetal life the spleen has the power of extensive blood formation. In the adult the spleen may undergo, in the presence of an injury to the bone marrow, a myeloid metaplasia; i. e., it can regain its fetal function under pathologic conditions. Whether the spleen may exert this power of blood formation in adult life under normal conditions is doubtful, though it is still an open question.

It thus has been shown in animals that hemoglobin katabolism can take place without the intervention of the liver, and that the spleen, in man, may carry on this function. In addition, it has been shown by experimental work on animals, that there is a close relation between the excretion of the bile pigments and the liberation of hemoglobin in the blood. The investigations carried out in man in such diseases as pernicious anemia, hemolytic jaundice, malaria, etc., have produced fur-

16. van de Bergh, A. A. H.: Nederlandsch. Tijdschr. v. Geneesk. **1**:1160, 1915.

17. Pearce, Krumbhaar and Frazier: The Spleen in Anemia, Philadelphia, 1918.

ther evidence of the derivation of the bile pigments from the products of hemolysis. Experimental evidence in man, however, in which measurable hemolysis has been produced in the circulation, with an immediate and continuous examination of the bile and blood, is conspicuously lacking.

It is our purpose, in this paper, to present further evidence regarding the katabolism of hemoglobin in man. It will be shown, first, that there is a direct relation between the liberation of hemoglobin into the plasma and the excretion of the bile pigments; second, that the liver is stimulated to increased functional activity by abnormal intravascular hemolysis; and third, that hemoglobin can be broken down in the blood vessels, capillaries and tissue spaces without the intervention of the liver or other organs.

The experiments which form the basis of this paper were conducted on two patients suffering from paroxysmal hemoglobinuria. It will be pertinent to insert at this point the following definition of this rare disease: "Paroxysmal hemoglobinuria is a chronic disease, due to syphilitic infection, manifesting itself in recurrent paroxysms of hemoglobinuria, and in characteristic constitutional symptoms. The blood of patients who suffer with this disease contains in latent form a specific hemolysin which becomes active when the blood is chilled, and produces the attacks."[18] Chilling of the blood to a temperature below 15 C. causes this specific hemolysin to become attached to the red cells. During subsequent warming at body temperature (37.5 C.) the hemolysin becomes active through the influence of the complement normally present in the blood, and hemolysis ensues. The amount of hemolysis is readily measured by the amount of free hemoglobin in the plasma, and is dependent on the length and severity of the chilling to which the blood is exposed.

One of the two cases (G. L. T) exhibited all the characteristic features of this striking disease. The patient was a congenital syphilitic. He showed in his blood the presence of the specific hemolysin peculiar to the disease, and was subject to attacks of hemoglobinuria on exposure to chilling. Antisyphilitic treatment had modified the course of the disease process, but at the time of our experiments the treatment had not been sufficient to free the patient from attacks. The second patient (A. L.) was also a congenital syphilitic. His sister had paroxysmal hemoglobinuria. Unlike his sister, however, he had never had an attack at all suggestive of this disease. His blood, nevertheless, showed the presence of the characteristic hemolysin, and both in vivo and in vitro, it was possible, by exposure to chilling, to demonstrate

18. Jones, B. B., and Jones, C. M.: Nelson's Loose Leaf Living Medicine, Washington, 1920.

definite hemolysis. This second case may thus be classified as a "potential" case of paroxysmal hemoglobinuria. It is of interest to note in this connection, that, in the blood of forty-five syphilitic patients who had no clinical symptoms of paroxysmal hemoglobinuria, we were able to demonstrate a similar hemolysin definitely in 6.6 per cent., thus approximately confirming the observations of Donath and Landsteiner,[19] Kumagai and Inoue,[20] and others.

The experiments conducted on these two patients consisted in the production of attacks of hemoglobinemia, with a subsequent study of the pigments in the blood, duodenal contents and urine. The condition studied was thus essentially intravascular hemolysis in man, uncomplicated by any other factor, such as liver damage, trauma, or by the introduction of any foreign substance into the circulation. Attacks of hemoglobinemia were brought about by immersing one or both of the patient's hands in ice water for several minutes, and then warming the chilled members. In none of the experiments was the chilling severe enough to cause more than a trace of hemoglobin to appear in the urine, and in two of the experiments hemoglobinemia only was produced.

Blood for examination was taken from an arm vein, either into a small amount of potassium oxalate solution, to prevent clotting, or allowed to clot at body temperature over a water bath. Special care was taken to prevent the occurrence of mechanical hemolysis.

The presence and amount of free hemoglobin in the blood was determined by spectroscopic examination of the oxalated plasma. The The number of dilutions with distilled water necessary to cause the disappearance of the characteristic absorption bands of hemoglobin from the spectrum was taken as the amount of free hemoglobin present in any given specimen of plasma. Inasmuch as bilirubin gives no characteristic absorption band in the spectroscope, its concentration in the blood plasma was determined by the methed described by Blankenhorn,[14] which consists merely in the dilution of the plasma or serum with distilled water until the yellow color disappears on comparison with a tube of distilled water. Here also the amount of bilirubin present was taken as the number of dilutions necessary to cause the disappearance of the yellow color. As a further test for bilirubin in the plasma, the Gmelin test with nitric acid was used. This test gives a positive reaction in the presence of relatively large amounts of bilirubin, but gives no characteristic color changes when hemoglobin alone is present. The Gmelin test, therefore, was used as a second method for determining the presence of abnormal amounts of bilirubin in the plasma or serum, especially when the characteristic yellow color was

19. Donath and Landsteiner: Ztschr. f. klin. Med. **58**:173, 1905.
20. Kumagai and Inoue: Münch. med. Wchnschr. **38**:361, 1912.

obscured by the additional presence of free hemoglobin. A positive Gmelin test is not obtained with specimens of normal blood. The presence of any quantity of free hemoglobin in the serum or plasma made it impossible to estimate accurately the amount of yellow pigment present. In such cases, when the yellow color was obscured by the presence of free hemoglobin, dilutions were carried out with distilled water until no color was left. A sample of the same plasma was also examined spectroscopically for free hemoglobin. Comparison between the amount of hemoglobin present, and the number of dilutions necessary to remove all traces of pigment, gave a rough estimation of the amount of bile pigment present. Inasmuch as the estimation of the amount of free hemoglobin and bilirubin in the plasma or serum were made by essentially different methods, it is obvious that any comparison between such estimations must be only an approximate one. The same holds true of any comparison made between the bilirubin and urobilin concentration in the duodenal contents, as will be pointed out. Other pigments than hemoglobin and bilirubin were not found in the blood.

The duodenal contents were obtained through an Einhorn tube, and were examined for the presence of the various bile pigments—bilirubin, urobilin, urobilinogen, cholecyanin, etc. Only the first three pigments were found. The position of the tip of the tube in the duodenum was confirmed by fluoroscope, and a free flow of bile was obtained by the use of a solution of magnesium sulphate, as described by Lyon.[21] Bilirubin values were obtained by a colorimetric method described by Hooper and Whipple [15] in their work on dogs with biliary fistulas. Briefly stated, their method consists in the treatment of the bile drainage with acid alcohol, and reading the resulting blue-green solution against a standard solution of copper sulphate and India ink in a Duboscq colorimeter. Urobilin and urobilinogen values were estimated by the method used by Wilbur and Addis, Schneider, and others. The method consists in treating a given quantity of duodenal contents (or feces) with an equal quantity of a saturated alcoholic solution of zinc acetate (Schlesinger's reagent), filtering, acidifying the filtrate with Erlich's solution (paradimethylaminobenzaldehydrochlorid), and after allowing this to stand in the dark for fifteen minutes, reading in the spectroscope. The number of dilutions with ethyl alcohol necessary to cause the disappearance of the characteristic absorption bands in the spectrum is taken as the value of the individual pigments. Urobilin and urobilinogen values were added together and expressed as one figure. As previously mentioned, the difference between the methods of estimating bilirubin and the other bile pig-

21. Lyon, B. B. V.: J. A. M. A. **73**:980 (Sept. 27) 1919.

ments made any comparison between the different estimates purely an approximate one. This method of studying the duodenal pigments is fully described in a separate paper.[13]

The presence of hemoglobin or urobilin in the urine was determined by the use of a spectroscope. Other bile pigments were tested for but none were found.

Measurement of the blood loss taking place following an attack of hemoglobinuria was determined by a series of red cell counts taken before and after the production of attacks. Such estimations were of course somewhat inaccurate, inasmuch as they did not take into account alterations in the peripheral circulation and the blood volume. For practical considerations, however, such determinations indicated the severity of an attack, as did the presence or absence of free hemoglobin in the urine.

Three separate experiments were performed on the two patients.

PROTOCOLS OF EXPERIMENTS

EXPERIMENT 1.—Patient G. L. T.

The results of this experiment are clearly shown in Chart 1. Samples of blood and urine were taken as normal controls before inducing an attack of hemoglobinemia. There was no free hemoglobin in either the blood or the urine, and the bilirubin content of the blood plasma was normal. Duodenal contents were taken at fifteen minute intervals for an hour and a half, in order to establish a normal pigment curve. The first peak shown in the chart came after the introduction of a 33 per cent. solution of magnesium sulphate into the duodenum, and was due partly to an increased flow of bile into the duodenum through the relaxed sphincter of Oddi, and partly to the addition of some of the concentrated bile in the gallbladder to the general flow. After the control figures had been obtained both the patient's arms were immersed in ice-water for five minutes, in order to produce intravascular hemolysis. Duodenal contents were then collected at intervals during the next three hours and a half. Samples of blood were also taken from an arm vein at varying intervals until there was no further hemoglobin in the plasma, and until the bilirubin contents of the plasma had practically returned to the normal level. Samples of urine taken at different times during the experiment failed to show any increase in bile pigment content, and at no time was there any evidence of hemoglobin.

Examination of Chart 1 shows clearly that there was an immediate and sharp rise in the hemoglobin content of the blood plasma, although prior to the attack there was no free hemoglobin present. Furthermore, before the attack there was a normal amount of bilirubin in the plasma as measured by its yellow color, and the Gmelin test was negative. The free hemoglobin observed shortly after the arm had been chilled indicated the immediate destruction of the patient's red cells within the blood vessels. The amount of free hemoglobin reached its peak within about four of five minutes after the attack had been produced. The plasma was bright red and no tests could be obtained for the presence of bilirubin. Twelve minutes after the patient's arms had been removed from the ice-water, a specimen of blood showed less than one-fourth the amount of free hemoglobin observed in the previous sample. The plasma was only slightly red, and there was a positive reaction to the Gmelin test for bile pigment. Furthermore, the color dilution of the plasma was increased over the previous specimen by over 50 per cent. Blood taken forty-five minutes after the attack showed a still further reduction in free

hemoglobin content, and the plasma was deep golden in color. The Gmelin test was strongly positive, and color dilution values were more than four times the original normal figure. From this point the pigments in the blood gradually returned to normal, so that in one hour and twenty minutes after the production of the attack of hemoglobinemia there was no free hemoglobin in the plasma. The bilirubin content had returned so near to normal that the Gmelin test was negative.

A study of the pigments in the duodenal contents showed no increase over the peak of the normal curve, obtained prior to the attack, until one hour after the production of the attack. At this time there was a marked rise in the bilirubin values. It will be noticed that this rise in bilirubin content of the bile

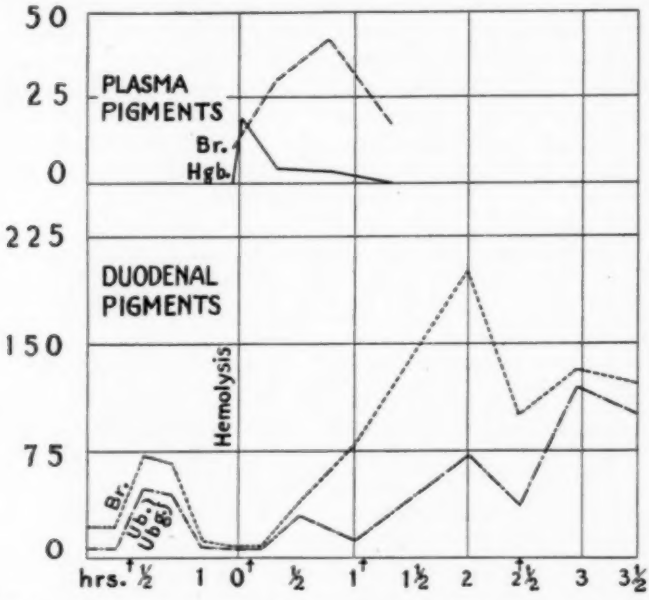

Chart 1.—The above curves of plasma and duodenal pigments are superimposed and have identical time relations. Points along the ordinates represent values of bilirubin (Br.), free hemoglobin (Hgb.), and combined urobilin and urobilinogen (Ub., Ubg.). Points along the abscissae represent specimens of plasma or duodenal contents obtained at the time intervals indicated. An attack of hemoglobinemia was produced at the point marked "Hemolysis." Magnesium sulphate solution (33 per cent.) was given at various times as indicated by arrows.

started at the time when the free hemoglobin had entirely disappeared from the blood, and when the bilirubin content of the plasma had already begun to return to the normal level. The bilirubin content of the bile continued to increase until it reached its highest concentration at a point two hours following the attack. From this point it gradually diminshed in amount, but three and one-half hours after hemolysis was produced the bilirubin concentration in the bile was still nearly twice the greatest amount obtained before hemoglobin was liberated into the circulation. Urobilin and urobilinogen values also

showed a marked increase, but the time of appearance of these pigments was later than that of bilirubin. At the end of two hours, when the bilirubin concentration had reached its peak, urobilin and urobilinogen values began to show a definite increase over the normal. From this point, however, they continued to increase until the greatest concentration of these pigments in the bile was reached about three hours after hemolysis had been produced. These pigments then gradually diminished in amount, although three and one-half hours after the induction of hemolysis their concentration in the bile was still about double the highest point reached in the control readings.

Repeated examinations of the urine revealed at no time the presence of any abnormal pigments.

Analysis of the above findings brings out the following points. An attack was produced in a patient, in which there was an immediate liberation of a large amount of hemoglobin into the circulation. Almost immediately following the attack the hemoglobin freed from the patient's red corpuscles reached its highest concentration in the circulation. At the end of twelve minutes the larger part of the free hemoglobin had been removed from the circulation and had been replaced by bilirubin, which appeared in amounts greatly increased over normal. As the hemoglobin diminished, the bilirubin content increased, until the latter reached its peak in about forty-five minutes. Both pigments gradually returned to normal, about one-half hour later, and as they approached normal the bilirubin content of the bile showed a marked increase. Accompanying this increase of bilirubin in the duodenal contents there was a similar rise in the lower bile pigments, urobilin and urobilinogen. This latter increase, however, proceeded at a much slower rate, and did not reach its peak until the bilirubin had already begun to return toward normal.

Here, then, is an orderly sequence of events, and the following deductions may reasonably be drawn. Following an uncomplicated attack of red cell destruction in man the hemoglobin liberated into the general circulation was rapidly changed to, or replaced by, an increased amount of bilirubin in the plasma. Inasmuch as there was no restriction on the circulation, it is evident that the liver, or any other organ, might have participated in this transformation of hemoglobin into bile pigments. As a matter of fact, however, there was no demonstrable response in the liver excretion until all the hemoglobin, and the greater part of the excess bilirubin had disappeared from the plasma. Such a finding seems to indicate that the change from hemoglobin to bilirubin might well have taken place merely in the blood vessels and capillaries. That there was a marked response on the part of the liver to the sudden excess of hemoglobin in the circulation is indicated by the elimination in the bile of a tremendous amount of bilirubin. This increase amounted to as much as three times the normal concentration of this pigment in the bile, and is clear evidence of a definite relation between the liberation of hemoglobin into the circulation and the excretion of bilirubin in the bile. Such an increase is also definite evidence of a stimulation of the liver to increased activity by the products of red cell destruction. The accompanying rise in concentration of urobilin and urobilinogen in the bile following the production of an attack of hemolysis indicates the close relation of these pigments to bilirubin, and thus indirectly to hemoglobin.

After a careful examination of the time relation between the appearance of an excess of bilirubin in the bile and the subsequent increase of urobilin and urobilinogen another point of interest is brought out concerning the origin of these last two pigments.[22] It will be noticed on Chart 1 that the peak of a bilirubin curve in the duodenal contents came approximately one hour before urobilin and urobilinogen were found in their greatest concentration. Furthermore, the peak of the latter pigments came within three hours of the beginning of the experiment. This rise in urobilin and urobilinogen values was clearly the result of a liberation of hemoglobin into the general circulation, and followed the increase of bilirubin in the bile by a definite but relatively short interval. The time interval elapsing between the appearance of excess bilirubin was obviously too short to allow of intestinal action upon the bilirubin excreted in the bile, and subsequent reabsorption of pigment via the portal circulation. Bacterial action, especially on protein molecules, is not marked until the lower portion of the small intestine and the upper portion of the large intestine is reached. In this experiment it is obvious that bacterial reduction of the excess bilirubin in the intestine could in no way account for the increased amounts of urobilin and urobilinogen in the bile, and is direct evidence against the early theory of the intestinal formation of urobilin and urobilinogen. The time element alone appears to exclude such a possibility. The logical assumption is, therefore, that these lower pigments were formed by the liver directly from the bilirubin which was a result of increased hemoglobin katabolism. The power of the liver to form not only bilirubin, but urobilin and urobilinogen, is clearly indicated. The results suggest that the formation of bilirubin may take place outside of the liver, but do not prove this conclusively, inasmuch as the blood determinations were all taken from the general circulation, from which the liver and other organs could not be excluded. With these considerations in view a second experiment was tried with two main objects: (1) to check the results of the first experiment, and (2) to produce evidence of the extrahepatic formation of bile pigment.

Experiment 2.—Patient, G. L. T.

The results of this experiment are shown in Chart 2. Control specimens of blood, duodenal contents, and urine were taken and examined as outlined in Experiment 1. An attack of hemoglobinemia was produced this time by immersing only the patient's left arm in ice-water. In order to study the changes taking place in the blood vessels, without the intervention of the liver or other organs, a tourniquet was applied above the elbow of the left arm before immersion, and was kept on this arm for twenty-five minutes. In this way the blood in the vessels, capillaries and tissue spaces in the lower

22. Urobilinogen, although present in increased amounts, was at no time found in great concentration.

left arm could be subjected to chilling and subsequent warming without mingling with the general circulation. Samples of blood were taken from the left arm several times before the removal of the tourniquet, in order to observe any changes taking place in the pigments while the local circulation was thus isolated. Specimens of blood were also taken from the right arm at similar intervals in order to ascertain whether there was any leakage of blood from the immersed arm past the tourniquet into the general circulation. Unfortunately, the tourniquet pressure was not sufficient to prevent some leakage, and the results, while more suggestive than in the first experiment, were still not conclusive. The chart showed a similar curve for the pigments in the blood plasma to that obtained in the previous experiment. It will be noted, however, that both the free hemoglobin and the bilirubin contents of the plasma reached a greater concentration than that obtained before. It also required a much longer period for these pigments to return to their original concentration in the blood. The higher values may be readily accounted for by the fact that the attack of hemolysis produced in this experiment was more severe than

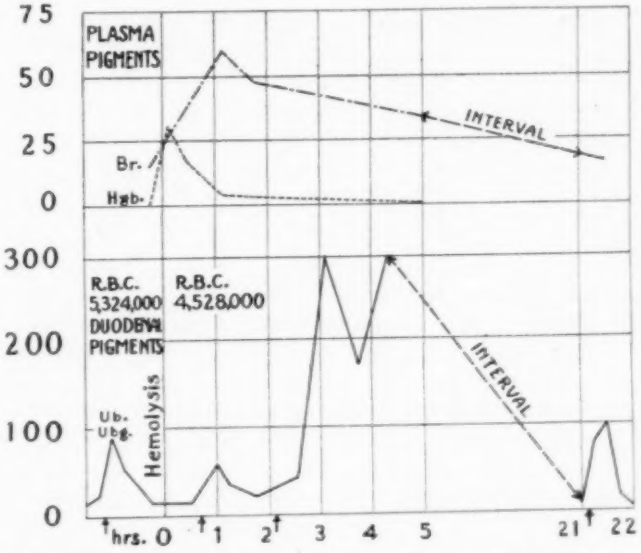

Chart 2.—Constructed in the same manner as Chart 1. The significance of the various pigments and the method of their determination is fully outlined in the text.

the previous one, as evidenced by the finding of traces of free hemoglobin in the first specimen of urine voided after the attack. Furthermore a large amount of the free hemoglobin in the vessels of the left arm was not released into the general circulation until the removal of the tourniquet, some twenty-five minutes after the attack of hemolysis was produced. Such a delay would naturally retard the complete katabolism of the various pigments. In this case the bilirubin content of the plasma did not return to normal until about twenty-one hours later.

As a means of determining the relative amount of blood destruction produced in this experiment duplicate red counts were taken from the peripheral

and general circulation before the immersion of the arm in ice-water, and shortly after the removal of the tourniquet. Before hemolysis was produced the red cell count was 5,394,000 per c. mm. Similar counts made almost immediately after the tourniquet had been removed averaged 4,528,000 per c. mm. In other words, the number of red corpuscles destroyed was roughly about 850,000 per c. mm. Such a figure does not take into account changes in the peripheral circulation or in blood volume, but permits at least a rough estimate of the severity of the attack.

The duodenal contents were collected as before, and determinations of urobilin and urobilinogen were made. The curve of bilirubin elimination was not estimated. This time, however, specimens were collected for four hours after the initiation of hemoglobinemia. The duodenal tube was then removed, but was reintroduced the following morning in order to determine approximately the length of time necessary for the duodenal pigments to return to a normal level. Blood examinations were made at the same time. Estimations of the duodenal pigments showed that they reached their peak in about three hours, but that they did not return to normal until about some twenty-one hours.

The results of this experiment confirmed the findings and conclusions of the first. In addition they afforded a rough estimate of the amount of blood destruction necessary to produce a given level of pigment values, both in the blood plasma and in the bile. In an attack of hemoglobinemia just sufficient to produce a trace of hemoglobin in the urine it apparently takes about twenty hours for the bile pigments in the plasma and bile to return to their former normal level. The experiment failed to give conclusive evidence of the extrahepatic formation of bile pigment.

EXPERIMENT 3.—Patient A. L.

The results are shown in the accompanying table. The purpose of the experiment was to obtain conclusive evidence that the bile pigments, or at least bilirubin, could be formed in the peripheral blood vessels and other tissues that occur in an extremity, without the intervention of the liver. Such a probability was suggested in both the previous experiments, but failure properly to isolate the peripheral arm circulation from the general circulation made any evidence obtained inconclusive. In this experiment the rubber arm band of a sphygmomanometer was applied to the patient's left arm above the bend of the elbow, and was used as a tourniquet. The systolic blood pressure of this patient was 118. Throughout the experiment the pressure on the arm was maintained above this systolic pressure with the result that the blood below the tourniquet was completely isolated from the rest of the general circulation. After a specimen of blood had been obtained as a normal control, the patient's left arm, with the tourniquet applied, was immersed in ice-water (temperature, 5 C.). In order to cause only a moderate amount of hemolysis the arm was kept in the water for a period of only two and one-half minutes. It was then withdrawn and covered with a warm blanket to supply the deficiency of body heat caused by the stasis of the peripheral blood. Specimens of blood were withdrawn from the arm circulation at intervals of three, twenty and thirty-three minutes after hemolysis had been produced. A specimen was then taken from the gneeral circulation before the removal of the tourniquet in order to prove that there had been no communication between the arm and the general circulation. The tourniquet was then removed and the blood from the arm circulation allowed to mingle with that of the general circulation. A final specimen was taken from the general circulation twenty minutes after the removal of the tourniquet.

The first specimen of blood taken after immersion of the arm (Specimen 2) showed a definite trace of free hemoglobin. The next sample of blood, taken twenty minutes after the beginning of the experiment, showed a large amount of free hemoglobin, so that the plasma was reddish yellow in color. The Gmelin test was negative. The delay in the appearance of the hemoglobin may be explained by the fact that, owing to the complete isolation of the arm from the general circulation, the temperature after immersion was well below that of the rest of the body. Inasmuch as the hemolytic reaction in paroxysmal hemoglobinuria takes place completely only after the blood has been returned to body temperature, it becomes evident that the slow return of the arm to body temperature greatly delayed the process of hemolysis. Specimen 4 was taken thirteen minutes later. The plasma was dark yellow in color, instead of having the strong reddish tinge observed in the previous specimen. Simple color dilution showed the same pigment content as in Specimen 3. The hemoglobin content, however, was less than half that observed in the previous sample. Furthermore, there was a definite positive Gmelin test. The tourniquet was then removed as the arm was very cold and cyanotic. Specimen 5, taken from the general circulation just before the tourniquet was removed, showed that no hemoglobin had entered the general circulation from the left arm. Specimen 6, taken from the general circulation about an hour after the attack of hemolysis was produced, and twenty minutes after Specimen 5, showed a trace of free hemoglobin, and in addition gave a doubtful Gmelin reaction.

The above findings may be summed up as follows: Intravascular hemolysis was produced in a very restricted portion of the circulation. Thus the products of hemolysis were completely isolated from the influence of the general circulation, or of any of the organs of the body. Free hemoglobin was liberated and reached its greatest concentration in the plasma in twenty minutes. Although still completely isolated, the free hemoglobin rapidly diminished in concentration. Accompanying this reduction in hemoglobin concentration there was a marked increase in the bilirubin content of the plasma, as indicated by a positive Gmelin test, and by a change in color of the plasma from a reddish yellow to a dark golden yellow. Inasmuch as no bile pigment had been introduced into the blood of the isolated arm circulation at any time it is evident that the free hemoglobin had undergone a transformation in the bilirubin in the local blood vessels, capillaries and tissue spaces. The absence of any trace of free hemoglobin in the general circulation before the removal of the tourniquet indicates that there was no communication between the process taking place in the arm and the rest of the body.

It will be noticed in the table that the hemoglobin content of the plasma in Specimen 6, taken from the general circulation twenty minutes after removal of the tourniquet from the left arm, is still about one-half the concentration in Specimen 4. Obviously the liberation of the free hemoglobin contained in the lower left arm into the blood of the general circulation, other things being equal, should result in a much greater dilution than that observed. A similar discrepancy

may also be noticed in a careful comparison of Charts 1 and 2. In Experiment 1 the free hemoglobin of the plasma obtained from the general circulation shortly after hemoglobinemia was induced was twenty-two dilutions. In Experiment 2 the hemoglobin concentration in the blood plasma taken from an almost completely isolated lower arm circulation, following a more severe attack of hemolysis, and resulting in the appearance of traces of hemoglobin in the urine, was only thirty dilutions. Such an apparent discrepancy between the amount of free hemoglobin observed in the general circulation and that noted in a restricted part of the circulation may be readily explained by a consideration of the mechanism taking place in paroxysmal hemoglobinuria. As has already been explained, complete hemolysis occurs only when the temperature of the chilled blood has returned to 37 C. In Experiments 2 and 3 the temperature of the arm in which the local circulation had been restricted by the application of the tourniquet did not return to normal for a considerable length of time. In Experiment 3, for example, the arm temperature, thirty-five minutes

Evidence of the Extrahepatic Formation of Bile Pigments *

Specimen of Plasma	Time Interval After Attack	Color of Plasma	Color Dilutions	Gmelin Test	Hemoglobin Dilutions
1	Control	Straw	12	0	0
2	3 minutes	Pink straw	20	0	2
3	20 minutes	Reddish yellow	45	0	9
4	33 minutes	Dark yellow	45	+	5
5	35 minutes	Straw	12	0	0
6	55 minutes	Pink yellow	35	±	2.5

* Explanation: Intravascular hemolysis was produced in the vessels of the lower left arm following the taking of Specimen 1. Specimens 1 to 4 inclusive were taken from the left arm, where the blood was cut off from the general circulation by the maintenance of a tourniquet with a pressure constantly above systolic blood pressure. Specimen 5 was taken from the general circulation before the tourniquet was removed from the left arm. Specimen 6 was taken from the general circulation twenty minutes after the tourniquet had been taken off the left arm.

after the induction of hemolysis, was still well below normal. As a result complete hemolysis did not occur in either Experiment 2 or 3 as long as the blood in the arm was isolated from the rest of the circulation. Only when the blood contained in the arm vessels was allowed to enter into the general circulation did the hemolytic complex become completely activated. Thus hemoglobin determinations in specimens of blood taken from the local arm circulation were relatively low, while those specimens taken from the general circulation after removing the tourniquet continued to show a relatively high hemoglobin concentration in the plasma because of a continuation of the hemolytic process.

Definite evidence is thus presented of the extrahepatic formation of bilirubin from hemoglobin in man. The process in this instance took place solely in the blood vessels, capillaries, and tissue spaces of the patient's left lower arm. Inasmuch as the process was entirely confined to these anatomic structures it seems logical to assume that the

principal if not the sole agents concerned in the transformation of hemoglobin into bilirubin were the cells of the vascular endothelium. Such a conclusion has already been made by Hooper and Whipple [15] in the case of animals. If such an assumption is true, it is logically suggested that the normal activity of the liver in the process of hemoglobin metabolism is due to the endothelial cells with which it is richly supplied, both in the blood vessels and sinuses, and in the so-called stellate cells of Kuppfer. While undoubtedly the transformation of bilirubin into the lower bile pigments is due to the activity of the parenchymal cells of the liver, it is evident that some, and possibly a large part of the first steps of hemoglobin katabolism may be carried on without the intervention of the hepatic parenchyma.

CONCLUSIONS

1. In the absence of complicating factors, varying degrees of blood destruction in man are accompanied by corresponding variations in the concentration of bile pigments in the blood plasma and bile.

2. In man, the liberation of excessive amounts of hemoglobin into the circulation results, first, in the rapid elimination of hemoglobin from the blood stream and its replacement by bilirubin; second, in the more gradual disappearance of excess bilirubin from the plasma; third, in the appearance of an increased amount of bilirubin in the bile; fourth, in subsequent diminution of bilirubin in the bile, and its replacement by increased amounts of the lower bile pigments, notably urobilinogen and urobolin; and fifth, in the gradual elimination from the bile of excessive amounts of the latter pigments. There is a definite time interval between each of these phenomena. The above process is probably only an exaggeration of the normal process involved in the metabolism of hemoglobin.

3. Experimental evidence in man suggests strongly that the bulk of this pigment elimination is normally carried on by the liver.

4. Under abnormal conditions, in man as well as in animals, free hemoglobin can be broken down, at least as far as the bile pigment bilirubin, in the blood vessels, capillaries, and tissue spaces, without the intervention of the liver or any other organ.

5. These experiments suggest that a large part of the transformation of hemoglobin into bilirubin could occur normally in the blood vessels. Possibly the greater portion of this change takes place in the blood vessels of the liver because of the vascularity of this organ.

6. The low bile pigments urobilin and urobilinogen can be formed in the liver, without the intervention of bacterial action in the intestine.

The writers wish to express their appreciation to Dr. Roger I. Lee and Dr. George R. Minot for extremely valuable criticisms and suggestions.

STUDIES OF THE CAUSE OF PAIN IN GASTRIC AND DUODENAL ULCERS II.

PERISTALSIS AS THE DIRECT CAUSE OF PAIN IN GASTRIC ULCERS WITH ACHYLIA AND IN DUODENAL ULCERS

LEO L. J. HARDT, M.D.
ROCHESTER, MINN.

For many years clinicians have been aware of the fact that not infrequently the symptoms of infection of the gallbladder and appendix and of achylia gastrica of unknown etiology may simulate those of typical gastric or duodenal ulcer. Since reflex pain may be indistinguishable from the true pain in ulcer, to what should this gastric pain, brought on by extragastric lesions, be attributed? Is there direct damage to the stomach and duodenum through this reflex mechanism?

In the consideration of the cause of gastric pain from gastric and duodenal ulcers or reflexly from an infected gallbladder, appendix, or achylia gastrica, two factors are of importance. On the one hand, is the question of acidity or hyperacidity and hypersecretion, and, on the other hand, variations in tonicity, intragastric tension, and peristalsis of the stomach and duodenum. Clinicians generally have been satisfied with the plausible explanation of hyperacidity and hypersecretion being the most likely cause of pain. As proof they administer alkalies which stop the pain, and quite logically they conclude that control of the pain and subsequent healing of the ulcer are mainly questions of neutralization. This view has been substantiated by Cannon [1] in his classical work on the acid control of the pylorus. His theory does not explain the emptying of the stomach in gastric achylia, the rapid exit of water and egg albumin, nor the observations of Spencer, Meyer, Rehfuss and Hawk,[2] that a 1 per cent. solution of sodium bicarbonate hastens the discharge f.om the normal human stomach.

The experimental work of Luckhardt, Phillips and Carlson [3] indicates very conclusively that the pylorus opens for the ejection of chyme when it is reached by powerful advancing rings of contractions and when tonicity of the stomach musculature is greatly increased.

1. Cannon, W. B.: The Acid Control of the Pylorus, Am. J. Physiol. **20**: 283, 1907.

2. Spencer, W. H.; Meyer, G. P.; Rehfuss, M. E., and Hawk, P. B.: Gastro-Intestinal Studies. XII. Direct Evidence of Duodenal Regurgitation and Its Influence on the Chemistry and Function of the Normal Human Stomach, Am. J. Physiol. **39**:459, 1915.

3. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Contributions to the Physiology of the Stomach. LI. The Control of the Pylorus, Am. J. Physiol. **1**:57, 1919.

The gastric contents entering the duodenum are usually acid to phenolphthalein, but rarely show the presence of free acid to dimethylamidoazobenzaldehyd.

Carlson,[4] Ginsburg, Tumpowsky and Hamburger[5] and Hardt,[6] working independently, have demonstrated, by means of kymographic records, various types of contractions and peristalsis of the stomach, which they concluded are the main factors in the causation of the pain of ulcer. New light was thrown on the etiology of pain, not only from gastric or duodenal ulcers, but also from achylia gastrica.

INVESTIGATION

Method.—The relation of gastric motility to pain was studied in twenty-five patients by the kymographic method. All patients were given a standard meal, consisting of two soft boiled eggs, two pieces of toast, two glasses of milk, and the juice of a grapefruit. From one to two hours later, two tubes were swallowed, a Rehfuss tube and a small rubber tube with a fine rubber balloon attached at one end and a chloroform manometer to the end which projected from the mouth. The balloon, held as closely as possible to the cardiac end of the stomach, was blown full of air; it was compressed according to the various types of contractions of the stomach, and thus air forced into the manometer caused the rider to record the variations in tonicity and the contractions on a slowly moving kymograph. These tracings were continued for from one to three hours, and at intervals of one-half hour from 15 to 30 c.c. of stomach contents was aspirated to determine the presence or absence and percentage of free and total acids. The twenty-five patients were divided into two groups:

Group 1.—This group comprises twenty patients with duodenal ulcers, the majority of whom came to the clinic during a quiescent period in their trouble. The diagnosis was based on the clinical history and confirmed by roentgen-ray examination. All these patients were treated medically by the Sippy method at the completion of the kymographic record. None of the patients whose kymogram showed only Type I contractions (Fig. 1) experienced pain. All of these patients during the course of experiment revealed adequate free acids ranging from 20 to 90 (in terms of one-tenth normal hydrochloric acid). Six

4. Carlson, A. J.: Contributions to the Physiology of the Stomach, XLIV. The Origin of the Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **45**:81, 1918.

5. Ginsburg, H.; Tumpowsky, I., and Hamburger, W. W.: Contributions to the Physiology of the Stomach, XXXV. The Newer Interpretation of the Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916.

6. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum. Gastric and Duodenal Contractions as the Direct Cause, J. A. M. A. **70**:837 (March 23) 1918.

of the patients in whom contractions of Type III (Fig. 2) or Type IV (Fig. 3) were recorded, experienced burning or gnawing pain similar to pain in ulcer, in practically every instance synchronous with the peristalsis, but as long as Type I contractions were recorded they were without pain.

The degree of acidity seemed to have little bearing on the pain. The acidity on the whole was lower at the time of the pain and active peristalsis than during the absence of pain and slight peristalsis.

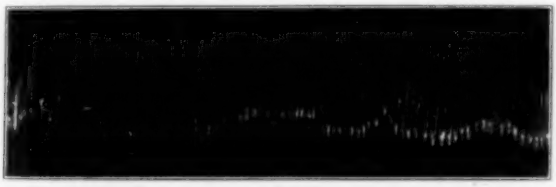

Fig. 1 (Case 147,732).—Type I contraction. Tonus variation or digestive peristalsis, without pain.

Group 2.—This group comprises five patients with achylia gastrica. Three patients were without pain and without any demonstrable pathologic condition, one patient had gastric ulcer and one had pain without any demonstrable pathologic condition. The three patients without pain had no definite epigastric distress other than a little bloating or a burning sensation. Two of them revealed only Type I contractions during the course of the experiment; but the third had definite

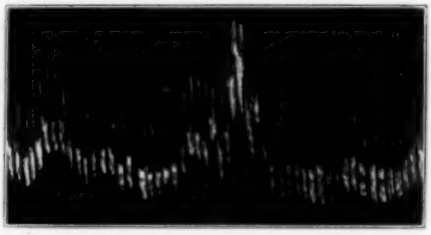

Fig. 2 (Case A351,625).—Type III contraction. Beginning hunger peristalsis, with pain.

Type II (Fig. 4) and Type III peristalsis. These three patients clearly show that normal tonus variations and peristalsis can be present in achylia gastrica. The patient with gastric ulcer (Case A147,732) had repeated gastric analyses which failed to reveal evidence of free acids. The typical epigastric pain of a gastric ulcer continued, pain coming on from two to three hours after eating, with relief by food, water, alkalis,

gastric lavage, and emesis. On several occasions during a period of distress, acid-free contents were washed out of the stomach and the patient obtained prompt relief. Kymographic tracings begun two hours after a test meal showed tonus variations without pain (Fig. 4); but gradually as the tonus variations were replaced by more active contractions of Type II and Type IV intermittent epigastric pain was complained of, which in almost every instance was synchronous with the peristalsis. The fifth patient (Case A254,365) had pain typical of ulcer, differing somewhat in that it continued for long periods without remission, but

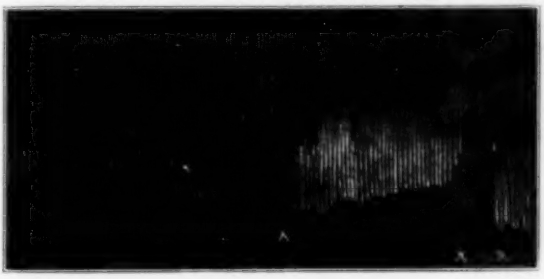

Fig. 3 (Case A356,604).—Type IV contraction. Vigorous hunger peristalsis, which is coincident with gnawing or burning pain.

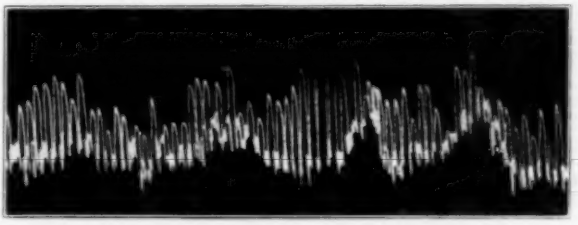

Fig. 4 (Case A254,365).—Type II contraction. Exaggeration of tonus variation which precedes the vigorous peristalsis; frequently associated with a moderate amount of pain.

no demonstrable pathologic condition. Several analyses of gastric contents failed to reveal any evidence of free acidity. At the time the patient experienced pain the kymograph recorded Type II (Fig. 4) and Type III (Fig. 2) contractions, the pain being absent during the period of slight tonus variations (Fig. 1).

REPORT OF CASES

Case 1 (A47,732).—*History.*—S. A. M., aged 49 years, first came to the Clinic, Dec. 11, 1915, complaining of epigastric pain three to four hours after meals. The attacks occurred in spells lasting from a few weeks to a month and remissions lasted from three to five months. Belching, drinking hot water,

milk, or cream had usually given relief. For three months beginning August, 1915, he had vomited nearly every night between 1 and 3 a. m.

Operation (Dec. 20, 1915).—This revealed a perforating duodenal ulcer extending into the pylorus, with adhesions to the head of the pancreas and with almost complete closure of the pylorus. Gastro-enterostomy and appendectomy were performed. Gastric analysis at this time revealed total acids 42 and free acids 30, with laboratory findings pointing to pyloric obstruction. The patient was free from symptoms for three months following operation.

Course.—From 1916 until the patient's second admission to the Clinic, June 19, 1921, he had frequent attacks of epigastric pain two to three hours after meals, which were relieved by emesis, food and alkalies. Roentgen-ray examination revealed a gastric ulcer.

At operation, June 27, 1921, scar tissue was found on the duodenum, but no ulcer within. An ulcer 1.5 cm. in diameter was located on the lesser curvature of the stomach, 3.75 cm. above the pylorus. The gastro-enterostomy was found to be patent and functioning. The ulcer was excised and the diagnosis confirmed by microscopic examination.

CASE 2 (A254,365).—*History.*—M. T., aged 25 years, first came to the Clinic Dec. 26, 1918. He complained of epigastric distress of a burning character one hour after meals and at midnight. The pains were usually relieved by eating. In addition he complained of diarrhea which was closely associated with the epigastric distress. Gastric analysis failed to reveal any free acidity. *Endameba histolytica* was found in the stools. He was given emetin treatments for five days and sent home with advice as to treatment of diarrhea.

Dec. 26, 1919, the patient returned, still complaining of frequent attacks of burning pain in the epigastrium. The pain would be present for three or four days and then disappear for a week. The diarrhea had cleared up. He was given bromids three times daily after meals.

Dec. 27, 1920, the patient again returned with identical gastric complaints. The bromids had given relief for six months. This time he was given dilute hydrochloric acid, fifteen minutes after meals.

April 19, 1921, the patient returned with epigastric pain which had not been relieved by the previous treatment with hydrochloric acid.

The stomach had been examined with the roentgen ray on each admission but no evidence of gastric or duodenal ulcer had been obtained. Repeated gastric analysis had failed to reveal any free acids.

At the last visit kymographic records were taken which showed that the pains were intermittent and coincident with the active peristalsis. Alkalies and tincture of belladonna gave relief.

COMMENT

The two groups of patients substantiate the theory of variations in tonicity and peristalsis as the main factor in the cause of gastric pain; the acidity is considered a secondary and in some cases not even a necessary finding, as in the two cases of achylia gastrica. That the motility and tonicity of the stomach is quite independent of the acidity is indicated by the cases of achylia in which all the normal contractions were obtained in the absence of acidity. Furthermore, emptying of the stomach was not interfered with, since in none of these cases were there the slightest symptoms or signs of retention.

The quiescent period is probably the result of a diminution in the degree and extent of the inflammatory process, together with a decrease in the tonicity and contraction of the gastric and duodenal musculature. The administration of food, alkalies, water, emesis and gastric lavage

temporarily produces this quiescent state, mainly through the inhibition of the peristalsis which is replaced by the nonpainful digestive peristalsis, described by Rogers and Hardt.[7] The acid in all probability merely exaggerates to some extent the pain resulting from the more vigorous peristalsis and pyloroduodenal spasms.

The logical therapy in cases of gastric and duodenal ulcer should, it seems, tend primarily to inhibit peristalsis. About 85 per cent. of the patients treated surgically in the Mayo Clinic have been cured of the ulcer or satisfactorily improved. It might be assumed from these results that surgical procedures inhibit the vigorous peristalsis for a period long enough to promote healing of the ulcer, or at least a subsidence of the more acute inflammatory process. It is hoped that in the future this assumption can be demonstrated more conclusively by the kymographic method.

CONCLUSIONS

1. Gastric ulcer may be present in patients with achylia and may produce all the clinical symptoms characteristic of ulcer. The pain is primarily due to the peristalsis acting on an irritable focus. All the medical measures by which gastric acidity is neutralized and suppressed also inhibit the gastric peristalsis and thus relieve the pain.

2. Patients with gastric achylia in the absence of any demonstrable organic lesion may reveal the normal tonus variations and peristalsis.

3. Patients with uncomplicated duodenal ulcer do not experience pain during the period of digestive peristalsis, even in the presence of an adequate acidity. Active peristalsis of the "hunger type" (Types III and IV) is essential in the production of pain.

---

7. Rogers, F. T., and Hardt, L. L. J.: Contributions to the Physiology of the Stomach, XXVI. The Relation Between the Digestion Contractions of the Filled, and the Hunger Contractions of the "Empty" Stomach, Am. J. Physiol. **38**:274, 1915.

THE SEAT OF THE EMETIC ACTION OF THE DIGITALIS BODIES *

ROBERT A. HATCHER AND SOMA WEISS
NEW YORK CITY

Emetics are divided commonly into two classes: (a) Those which irritate certain nerve endings in the gastric mucous membrane; (b) those which stimulate the vomiting center in the medulla directly.

Hatcher and Eggleston [1] showed that emesis follows the intravenous injection of any one of the several digitalis bodies in dogs, even after the removal of the gastro-intestinal tract, and while they considered it possible that vomiting is due to a reflex arising in some peripheral structure, such as the esophagus, they came to the conclusion that all the evidence available points to the vomiting center as the seat of the emetic action of all of the digitalis bodies.

The fact that these bodies differ so widely in their chemical composition directed our attention to the coincidence that every member of the group shows a greater or less parallelism between its cardiac and emetic activities, though the several members of the group differ widely one from another with reference to the intensity of both of these actions, suggesting a common seat, and we have sought to determine whether the vomiting which digitalis bodies induce is indeed of cardiac origin.

It is also of especial interest that emesis and cardiac standstill may be induced within a few seconds after the intravenous injection of a large dose of digitoxin but that neither of these effects can be induced nearly so quickly by the largest doses of ouabain.

We have used crystalline ouabain (sometimes called crystalline strophanthin) in the larger number of our experiments because it is a typical digitalis body of uniform purity, is readily soluble in water, and it lends itself to studies such as we planned. We have also used amorphous strophanthin, digitoxin, digitalein and tincture of digitalis in those experiments which we consider crucial.

The digitalis bodies leave the circulation rapidly after their intravenous injection,[2] and only traces of the poisons can be found in the

---

* An abstract of this paper was presented before the Society for Experimental Biology and Medicine Oct. 19, 1921.

* From the Laboratory of Pharmacology of Cornell University Medical College.

* This work was carried out under the auspices of the Therapeutic Research Committee of the Section on Pharmacy and Chemistry of the American Medical Association.

1. Hatcher and Eggleston: The Emetic Action of the Digitalis Bodies, J. Pharmacol. & Exper. Therap. **4**:113 (Nov.) 1912.

2. Hatcher and Eggleston: Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, J. Pharmacol. & Exper. Therap. **13**:433, 1919.

blood after a few minutes, a fact of which we made use in the preliminary experiments of this investigation. In these experiments we tied or compressed the carotid and vertebral arteries, in order to diminish the circulation in the medulla, after which an amount of a digitalis body equal to a little more than the average emetic dose was injected intramuscularly or into the femoral vein. Emesis resulted in nearly every case though it is certain that less of the poison reached the vomiting center than could have reached it had there been no interference with the circulation.

Vomiting occurred in one experiment within two minutes after beginning the intravenous injection of ouabain and at the moment when an amount equal to about twice the average emetic dose had been injected, though emesis was delayed in the greater number of the experiments. This delay was almost certainly due in part to delayed absorption after intramuscular injection, and this in turn to the fact that the animals were somewhat depressed.

The cerebral circulation of the dog is said to become nearly normal soon after the carotid and vertebral arteries are tied, but this is not true of the cat. The animals usually slept or remained drowsy after the operation of tying the vessels, and further evidence that the circulation in the brain of the cat is greatly diminished by tying these arteries is afforded by the fact that the internal and external jugular veins were severed in one of these experiments without the loss of a drop of blood, and the blood escaped slowly when the carotid artery was cut across.

The results of these experiments are not conclusive because we cannot be absolutely certain that all of the poison had left the blood stream before emesis occurred and the delay in the onset of vomiting possibly may have permitted a fairly large amount to reach the medulla. The onset of emesis within two minutes after beginning the injection of ouabain in the first experiment, and at a time when the total amount injected was equal to only about twice the average emetic dose, affords strong evidence that vomiting was not due to a direct action on the medulla, because the interference with the circulation prevented the poison from reaching the medulla in an amount comparable to that which would reach it in the normal animal after an emetic dose.

An interval of twenty-four hours had been allowed to elapse after the operation and before the ouabain was injected in the first experiment, however, and it is possible that the circulation was partially reestablished during that interval, though the condition of the animal did not indicate that the circulation was normal. In the remaining experiments of this series the drugs were injected after the lapse of a

period which was considered necessary for complete recovery from the effects of the anesthetic. The protocols in brief of two experiments will be given.

PROTOCOLS OF EXPERIMENTS WITH OUABAIN

EXPERIMENT 1.—Female cat, weight 3.8 kg.; anesthetized with ether; the carotid arteries tied at a point about 3 cm. above the level of the sternum; the vertebral arteries tied near their origin; wound closed with sutures.

4:40 p. m.: Animal released; sleeps at once.
4:50 p. m.: Lifts head; wakens; soon sleeps; rapid respiration.
5:40 p. m.: Asleep but moves frequently.
Following day:
9:00 a. m.: Sits up; disturbed equilibrium.
3:25 p. m.: Femoral vein connected with buret for injection.
3:30 p. m.: Start injection of ouabain 1:10,000.
3:32 p. m.: Emesis; 0.13 mg. ouabain per kilogram of weight injected. Animal destroyed.

EXPERIMENT 2.—Male cat, weight 3.58 kg. Operation as in preceding experiment except that chloroform was used to induce anesthesia.

3:10 p. m.: Animal released.
3:35 p. m.: Sleeps quietly.
3:45 p. m.: 0.075 mg. ouabain per kg., 1:10,000, injected intramuscularly.
4:08 p. m.: Nausea followed almost at once by vomiting.

Following day: Animal in partial stupor; killed with chloroform; respiration markedly diminished; difficult to kill animal even with chloroform applied to nose on cloth.

Subsequent experiments were designed to compare the effect of permitting the drug to act on the vomiting center but not on the rest of the body, with that seen when the poison was allowed to enter the general circulation but not to reach the vomiting center.

In five experiments the carotid and vertebral arteries were tied or compressed, and the brain, with the vomiting center, was perfused for periods varying from five to fifteen minutes through the carotid arteries and jugular veins with defibrinated blood to which ouabain had been added in amounts varying from a small fraction of the average emetic dose to one that caused convulsions. In no case did vomiting occur nor were any symptoms of nausea observed after the animal was released.[3]

Five experiments were performed in the manner just described, except that the ouabain was injected into the femoral vein while the brain was being perfused with unpoisoned defibrinated and diluted blood, the perfusion being continued for periods of ten minutes, during which time all but traces of the poison left the circulation. The brain was perfused at a pressure greater than that of the general cir-

3. We employed a modified Langendorff apparatus; the temperature of the perfused fluid was kept at 37 C.; the pressure was regulated by means of compressed oxygen or air and a mercury valve.

culation, and we are fairly certain that no more than traces of the poison (if any) reached the medulla during the period of perfusion, though we could not measure the pressure in the circle of Willis at that time. Three of these five animals vomited; one showed unmistakable signs of nausea, and one showed some signs of nausea but these two did not vomit, because they were much depressed. The vertebral arteries were intact in two of these experiments but the results did not differ materially from those in two experiments in which they were tied.

Every one who has perfused the brain of the living animal appreciates the difficulties which are involved in the attempt to secure an approximately normal condition of the animal during the procedure, and we shall not enter into a discussion of the details of these experiments. We should be unwilling to base our conclusions concerning the seat of the emetic action of the digitalis bodies on the results of the perfusion experiments alone, but we can say that these results are in harmony with those obtained in other experiments which afford conclusive evidence that the digitalis bodies do not induce emesis through a direct action on the medulla. Those animals which were used in this series of experiments and which did not vomit after the injection of ouabain intramuscularly or into the femoral vein were so greatly depressed that emesis could not be expected to occur.

It is well known that Thumas [4] described an area measuring about 5 mm. in length and about 2 mm. in width, situated in the floor of the fourth ventricle and extending to a point about 2 mm. posterior to the calamus scriptorius, which he called the vomiting center. Thumas found that destruction of the tissue lying within this area inhibits vomiting, and that the application of apomorphin hydrochlorid to this area causes emesis in dogs. We have found that the application at this point of as little as 0.000,1 mg. apomorphin hydrochlorid for every kilogram of body weight causes emesis in dogs, and that larger doses cause vomiting within a few seconds.

The experiment is performed in the following way: The animal is anesthetized with chloroform and secured with the belly resting on the operating board; the base of the skull is exposed by incision; a button of bone is removed by means of a trephine having a diameter of six millimeters; the opening is enlarged slightly by chipping the bone; the dura mater is incised at the margin of the cerebellum; the wound is closed with a pledget of cotton soaked in phenol solution in oil and the animal is released. When the animal has recovered from

4. Thumas, L. J.: Ueber das Brechcentrum und über die Wirkung einiger pharmakologische Mittel auf dasselbe, Virchows. Arch. f. path. Anat. **123**:44, 1891.

the effects of the anesthetic, it is replaced on the board (or, in some cases, it stands on the table); the tissues are pulled aside and any blood or spinal fluid is removed with a pledget of cotton; the solution to be tested is dropped onto the area from a syringe graduated to 0.01 c.c., or the solution is dropped onto a very small pointed camel's hair brush with which it is painted onto the surface. It is important that general anesthesia be avoided at this time, and the use of the phenol in oil, applied to the edges of the wound, prevents pain.

Cats and dogs usually bear the operation well and appear normal as soon as they recover from the effects of the anesthetic. Ether was used in one of our experiments in which the drug was applied on the day following the operation, but chloroform was used in the other experiments because it is much less prone to cause vomiting. None of our animals vomited from the effects of the operation or from those of the chloroform. Troublesome hemorrhage from the diplöic vessels commonly follows the use of a trephine of greater diameter than that mentioned. Some of our experiments were performed with practically no loss of blood. Physiologic solution of sodium chlorid was dropped onto this area in control experiments and was found to be without perceptible effect.

We have sought to determine whether the digitalis bodies induce vomiting after direct application to the vomiting center, and ouabain, amorphous strophanthin, digitoxin and digitalein were applied to this area, but in none of the experiments of this series were we able to induce nausea or vomiting in this way, though widely varying amounts of the poisons were used. When very large doses of these drugs are applied to the center, they cause death without inducing emesis, and the application of moderately large, but not fatal, doses also appears to cause depression of the vomiting center, for emesis cannot then be induced by the intramuscular injection of ouabain.

The direct application of small amounts of the digitalis bodies to this area does not have any perceptible effect on the vomiting reflex, and the intramuscular injection of ouabain then causes emesis precisely as it does in the normal animal. While we speak of the amounts thus applied as small, since they are far less than the amounts required by intravenous injection to cause vomiting in the normal animal, they are actually much larger than those which can come into contact with the tissues of this area after the intravenous injection of an emetic dose and before vomiting takes place. The tissue embraced within the area described by Thumas constitutes approximately 1/75,000 of the total weight of the dog, and since vomiting frequently follows the intravenous injection of ouabain or digitoxin within two or three

minutes, it is evident that only a minute fraction of the total amount injected can come into contact with the vomiting center before emesis takes place.

The protocols in brief of four experiments are given. The first of these shows that armorphous strophanthin is absorbed into the general circulation, for the effects were typical except for the absence of nausea and vomiting, and that it causes depression of the vomiting mechanism. The second experiment shows that digitoxin also induces depression of the vomiting mechanism, since the intramuscular injection of a fatal dose of ouabain then failed to cause emesis. The third experiment shows that the application of a small amount of ouabain is without influence on the vomiting reflex, and the fourth shows that the application to this area of a moderate amount of ouabain causes depression or paralysis of the vomiting mechanism, since the intramuscular injection of very large doses of ouabain then failed to induce emesis. The result in this experiment is of interest in that the animal lived thirty-six minutes after the first intramuscular injection of an amount of ouabain equal to nearly three times the average fatal dose, and that it lived twenty minutes after the second injection, made sixteen minutes after the first injection, having received a total of nearly eight times the average fatal dose. It would appear that the depression induced delays the absorption of the drug from the intramuscular tissues.

The results of these experiments in which the poison was applied directly to the vomiting center point almost conclusively to the fact that ouabain does not induce emesis through any direct action on the medulla, and the absorption of a fatal dose after its application to the floor of the fourth ventricle without the production of nausea is of especial interest.

PROTOCOLS OF EXPERIMENTS

Experiment showing absorption of amorphous strophanthin after its application to the floor of the fourth ventricle.—Male cat, weight, 2.3 kg. Chloroform administered for anesthesia.

11:08 a. m.: Operation completed, animal released.
1:30 p. m.: Animal ate meat.
2:30 p. m.: 0.5 mg. amorphous strophanthin per kg. in 20 parts of physiologic solution of sodium chlorid applied to the floor of the fourth ventricle; immediate depression; animal unable to stand.
2:49 p. m.: Respiration irregular.
3:05 p. m.: No nausea; death.

Experiment showing depression of the vomiting mechanism following the application of a moderate amount of digitoxin to the floor of the fourth ventricle.—Male cat, weight 4.4 kg.; chloroform administered for anesthesia.

11:45 a. m.: Operation completed.
2:25 p. m.: Water administered through a stomach tube.
2:31 p. m.: 0.002 mg. digitoxin per kg. in 1,000 parts mucilage applied to floor of fourth ventricle; animal released; condition excellent.

2:48 p. m.: No perceptible effect; 0.45 mg. ouabain per kg. of weight injected intramuscularly.
3:03 p. m.: No symptom of nausea; convulsions and death.

Experiment showing that the application of a small amount of ouabain to the floor of the fourth ventricle is without perceptible effect on the vomiting mechanism.—Female cat, weight, 2.24 kg.; chloroform administered for anesthesia.

2:10 p. m.: Operation completed.
2:30 p. m.: 0.005 mg. ouabain per kg. in 10,000 parts physiologic solution of sodium chlorid, applied to the floor of the fourth ventricle.
3:00 p. m.: No symptoms of nausea.
0.2 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
3:15 p. m.: Emesis, repeated.
3:20 p. m.: Convulsion and death.

Experiment showing the depressant action of a moderate amount of ouabain on the vomiting mechanism following its application to the floor of the fourth ventricle.—Female cat, weight, 2.9 kg.; chloroform administered for anesthesia; operation as preceding.

3:15 p. m.: Animal appears normal.
3:27 p. m.: 0.01 mg. ouabain per kg. in 500 parts physiologic solution of sodium applied to the floor of the fourth ventricle; respiration rapid.
4:30 p. m.: Respiration about normal.
4:49 p. m.: No symptom of nausea.
0.33 mg. ouabain per kg. intramuscularly.
5:05 p. m.: 0.66 mg. ouabain per kg. intramuscularly.
5:18 p. m.: Walks normally; diarrhea.
5:25 p. m.: No symptom of nausea; convulsion and death.

It is well known, of course, that the heart is supplied not only with nerve fibers from the vagus, but also with fibers from the sympathetic which pass through the stellate ganglia to the sympathetic chain of ganglia, and we found that cutting the cord above the level of the second thoracic vertebra (which prevents impulses from passing from the heart to the medulla by way of the sympathetic) usually prevents nausea and vomiting after the administration of digitalis bodies.

Section of the cord below the level of the fifth thoracic vertebra has no perceptible effect on the emetic action of the digitalis bodies. This operation does not interfere with afferent impulses from the heart, hence these results have a certain value only in connection with those in which the cord was cut at a higher level.

Since the emetic action of the digitalis bodies is sometimes abolished by section of the cord above the level at which the sympathetic fibers from the heart enter, and since atropin does not affect this action, we did not anticipate that vagotomy would influence it, nevertheless we undertook to determine the effect of this operation.

A cannula was placed in the trachea and the vagi were cut at the level of the sixth cervical vertebra, after which the injection of ouabain invariably caused vomiting in four experiments in the cat.

Removal of the stellate ganglia [5] alone interfered with the emetic action of ouabain in some of these experiments, and removal of the ganglia together with cutting of the cardiac branches of the vagus prevented the appearance of symptoms of nausea almost invariably, after the administration of digitalis bodies, but mercuric chlorid still caused emesis promptly. In one experiment of this type, however, nausea followed the injection of digitalis, but a necropsy on the cat showed that the sympathetic cardiac nerve gave off three small branches to the sympathetic chain at a point between the heart and the stellate ganglion, consequently the removal of the ganglia did not prevent the passage of impulses from the heart through the sympathetic to the medulla in this experiment. The sympathetic nerve shows many irregularities in different individuals, and care is necessary in the interpretation of the results of experiments in which it is involved.

We believe that the results of these experiments justify the conclusion that when the nerve supply to the heart is intact the injection of a digitalis body causes emesis if the animal is in good general condition, but that the digitalis bodies are incapable of inducing nausea or vomiting when all of the nervous connections between the heart and the medulla are cut, though mercuric chlorid still causes vomiting exactly as it does in the normal animal.

This would indicate that the emetic impulses to which ouabain (or digitalis) gives rise do not traverse the same afferent path, or paths, which the afferent emetic impulses resulting from the action of mercuric chlorid traverse, or, to express it more accurately, mercuric chlorid appears to give rise to emetic impulses which reach the medulla through paths other than, or in addition to, those traveled by the emetic impulses which digitalis bodies induce.

Poisons are widely distributed in the vegetable kingdom, and it is evident that animals (as well as man) often take them with their food. We are so accustomed to seeing vomiting and diarrhea result from the irritant action of poisons (including under that term all harmful substances, such as indigestible food) that we are prone to lose sight of the fact that the stomach and intestine are not the only organs of the body which require protection from injury due to ingested poisons, and the heart, liver, lungs, kidneys and nervous system are attacked by certain poisons which have no injurious action on the stomach. The latter probably has developed a greater range of tolerance than any of the other organs, and it would be remarkable if Nature had provided such a complex reflex as that necessary for vomiting for the protection

5. The operation which we employed for the removal of the stellate ganglia is that described by E. Cyon [6] (6. E. Cyon: Methodik der physiologischen Experimente and Vivisectionen, Giessen, 1876, p. 174) which does not involve the opening of the chest.

of the stomach while leaving other, and more vital, organs having a similar innervation unprotected, and vomiting effectually protects the heart against the further absorption of poisons no less than it protects the stomach.

Impulses appear to pass upward from the heart to the medulla chiefly by way of the sympathetic, and to a less, though probably variable, extent, by way of the vagus. When the sympathetic alone is cut the administration of ouabain usually fails to induce nausea or vomiting. This may be due to the fact that the impulses passing upward by way of the vagus are usually insufficient to set up the vomiting reflex, or it may be that in those cases where vomiting is not elicited by the digitalis bodies after the sympathetic has been cut the vagus carries no fibers concerned with this vomiting reflex. It is significant, at any rate, that vagotomy alone does not prevent emesis after the injection of the digitalis bodies and that Eggleston [7] found that atropin does not interfere with emesis induced by digitalis, though it does inhibit that caused by pilocarpin.

In order to show that the cutting of the nerve paths from the heart, and not the disturbance due to the operative procedure, interfered with emesis, we conducted several experiments in which the celiac plexus was removed and the vagi were cut at the level of the diaphragm before the digitalis bodies were administered. This operation is more severe than that involved in the removal of the stellate ganglia and cutting the vagi in the neck, and some of the animals were so depressed that one could say with confidence that vomiting could not be induced by any digitalis body. Digitoxin was injected into two of these animals despite their being greatly depressed, because it seemed possible that the drug might induce emesis.

We repeated the experiment on seven cats which bore the operation with less depression, and all of these vomited or showed unmistakable signs of nausea, and we can say that the removal of the celiac plexus and cutting the vagi at the level of the diaphragm do not interfere with the emetic action of the digitalis bodies except in those cases in which the operation causes severe depression. With improved operative technic there was less depression and three of the last four animals of this series vomited while the fourth showed unmistakable signs of nausea.

Inasmuch as the animals in which the vagi were cut and those used in the last series of experiments behaved like normal animals (except for the depression) toward the digitalis bodies, there is no obvious need

7. Eggleston: The Antagonism between Atropin and Certain Central Emetics J. Pharmacol. & Exper. Therap. **9**:11 (Oct.) 1916.

of giving the protocols of the experiments, but condensed protocols of experiments of the other types are given.

The tabulated results of all experiments show that thirty-five of the animals which received digitalis bodies or mercuric chlorid vomited or gave unmistakable signs of nausea, and that the result in one of these was doubtful. Thirty of these actually vomited; four showed unmistakable signs of nausea but did not vomit after the severe operation for removal of the celiac plexus and vagotomy. One of these four, and the other one which failed to vomit, had only average emetic doses of ouabain, and such doses sometimes fail to induce emesis in normal animals. The typical signs of nausea—frequent chewing and swallowing of saliva—are as unmistakable as vomiting itself. When the animal licked its lips only infrequently, even though repeatedly, it was counted as doubtful. In none of the forty-four experiments in which the results are recorded as negative was there any symptom of nausea.

Protocols of experiments showing the effect of section of the cord on the emetic action of ouabain in the cat. 1. Female cat, weight, 1.7 kg.; chloroform administered for anesthesia.

2:20 p. m.: Spinal cord severed between the first and second thoracic vertebra; no interruption of respiration: fore legs normal, hind legs paralyzed.
2:30 p. m.: Condition fair.
4:15 p m.: 0.15 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
4:36 p. m.: 0.1 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
5:20 p. m.: 0.05 mg. ouabain per kg. in 10,000 parts of physiologic solution of sodium chlorid injected intramuscularly.
5:25 p. m.: No evidence of nausea; convulsions and death.

2. Female cat, weight, 2.30 kg.; chloroform administered for anesthesia.

3:30 p. m.: Spinal cord severed between the sixth and seventh thoracic vertebra; slight hemorrhage.
4:10 p. m.: 0.2 mg. ouabain per kg. in 5,000 parts physiologic solution of sodium chlorid, injected intramuscularly.
4:20 p. m.: Vomiting.
4:25 p. m.: Convulsions and typical death.

Protocols of experiments showing effect of extirpation of the stellate ganglia and vagotomy. 1. Male cat, weight 1.12 kg.; chloroform administered for anesthesia.

12:10 p. m.: Operation for removal of both stellate ganglia; cannula into the trachea; vagi cut.
12:25 p. m.: 1.0 mg. digitoxin per kg. in 2,000 parts physiologic solution of sodium chlorid injected intramuscularly; rapidly developing depression.
1:34 p. m.: No symptoms of nausea have developed; convulsion.
1:36 p. m.: Death; necropsy shows complete extirpation of both ganglia.

2. Male cat, weight 1.64 kg.; chloroform administered for anesthesia.

3:10 p. m.: Completed operation as in preceding experiment.
3:18 p. m.: Condition excellent.

TABLE 1.—Showing the Effect of the Application of Digitalis Bodies to the Floor of the Fourth Ventricle (the Vomiting Center of Thumas) in the Cat

Substance Used	Amt. per Kg. in Fractions of a Mg.	Result
ouabain	0.01	great depression
ouabain	0.01	no perceptible effect
ouabain	0.01	depression of vomiting center *
ouabain	0.05	no perceptible effect
ouabain	0.1	no perceptible effect
ouabain	0.3	death
ouabain	0.005	no perceptible effect * *
ouabain	0.005	no perceptible effect * *
ouabain	0.005	no perceptible effect * *
ouabain	0.015	depression of vomiting center *
ouabain	0.001	no perceptible effect †
ouabain	0.0065	no perceptible effect
ouabain	0.45	death
am. strophanthin	0.000,67	no perceptible effect * *
am. strophanthin	0.01	no perceptible effect * *
am. strophanthin	0.5	death
digitoxin	0.01	depression of vomiting center *
digitoxin	0.002	depression of vomiting center *
digitalein	0.015	no perceptible effect * *

* The intramuscular injection of a digitalis body later failed to induce emesis, showing that the vomiting center was depressed.

* * The intramuscular injection of a digitalis body later induced emesis, showing that the vomiting center was not paralyzed.

† A dog was used in this experiment.

TABLE 2.—Showing the Effect of Extirpation of the Stellate Ganglia Alone, and with Vagotomy, on the Emetic Action of the Digitalis Bodies in the Cat

Substance Used	Am. per Kg. in Mg.	Mode of Administration	Nausea or Vomiting
EXTIRPATION OF THE STELLATE GANGLIA ALONE †			
ouabain	0.3	intramuscularly	—
ouabain	0.5	intramuscularly	—
digitoxin	1.5	intramuscularly	+
tinct. digitalis	1000.0	intravenously	—
mercuric chlorid	50.0	by stomach	+
tinct. digitalis	1000.0	intravenously	+
EXTIRPATION OF THE STELLATE GANGLIA WITH VAGOTOMY			
digitoxin	1.0	intramuscularly	—
digitoxin	1.2	intramuscularly	—
strophanthin	0.4	intramuscularly	—
strophanthin	0.5	intramuscularly	—
tinct. digitalis	1000.0	intravenously	—
mercuric chlorid	50.0	by stomach	+
mercuric chlorid	50.0	by stomach	+

* The + sign indicates that nausea or vomiting occurred; the — sign indicates that they were absent.

† There was incomplete extirpation of the stellate ganglia in three experiments, and in these nausea and vomiting occurred. They are not tabulated here but they are included in the table giving the summary of results of all of the experiments.

3:25 p. m.: 50 mg. mercuric chlorid per kg. in 1,000 parts of water administered through stomach tube.
3:28 p. m.: Retching.
3:46 p. m.: Typical nausea and vomiting; animal destroyed; necropsy showed complete extirpation of both stellate ganglia.

Depression of the vomiting center could be determined only by the subsequent intramuscular or intravenous injection of an emetic dose of ouabain or other digitalis body. This test was not made in every experiment and it is probable that the vomiting center was depressed in several of those cases where no perceptible effect is recorded. General depression always tends to inhibit emesis.

TABLE 3.—SUMMARY OF THE RESULTS OF EXPERIMENTS DESIGNED TO DETERMINE THE SEAT OF THE EMETIC ACTION OF THE DIGITALIS BODIES

	Animal	Nausea or Vomiting +	—
I. *Carotid and Vertebral Arteries Tied:*			
1. Ouabain injected	cat	5	0
2. Digitoxin injected	cat	2	2*
3. Controls; no poison used	cat	0	5
II. *Perfusion of the Brain and Vomiting Center:*			
1. Ouabain added to perfused fluid	cat	0	5
2. Ouabain injected into femoral vein	cat	5	1?
3. Controls; no poison used	cat	0	3
III. *Digitalis Bodies Applied to Vomiting Center Directly:*			
1. Ouabain	cat	0	8
2. Ouabain	dog	0	2
3. Digitoxin	cat	0	2
4. Digitalein	cat	0	1
5. Amorphous strophanthin	cat	0	3
IV. *Section of the Cord:*			
(a) above the level of the second thoracic vertebra:			
1. Ouabain injected intramuscularly	cat	0	2
2. Pilocarpin injected intramuscularly	cat	1?	1
3. Mercuric chlorid by stomach (control)	cat	2	0
(b) section below the level of the fifth thoracic vert.:			
1. Ouabain injected intramuscularly	cat	2	0
V. *Vagi Cut About the Level of the Sixth Cervical Vertebra:*			
1. Ouabain injected	cat	4	0
2. Mercuric chlorid by stomach (control)	cat	1	0
VI. *Extirpation of the Stellate Ganglia:*			
1. Ouabain injected	cat	0	2
2. Digitoxin injected	cat	1	0
3. Tincture digitalis intravenously	cat	3‡	1
4. Mercuric chlorid by stomach (control)	cat	1	0
VII. *Extirpation of the Stellate Ganglia and Vagotomy:*			
1. Digitoxin intramuscularly	cat	0	2
2. Amorphous strophanthin intramuscularly	cat	0	2
3. Tincture digitalis intravenously	cat	1†	1
4. Mercuric chlorid by stomach (control)	cat	1	0
VIII. *Extirpation of the Celiac Ganglion with Vagotomy:*			
1. Ouabain intramuscularly	cat	2	0
2. Digitoxin intramuscularly	cat	5	2*

* These animals were much depressed.
‡ The extirpation was incomplete in two experiments.
† There was an abnormality of the sympathetic nerve.

While the present discussion is concerned primarily with the problem of the seat of the emetic action of the digitalis bodies, we wish to offer certain suggestions relating to the physiology of vomiting, and to state that we are now trying to secure evidence to determine whether our view is correct, for this problem is intimately concerned with that of the emetic action of the digitalis bodies.

We believe that the vomiting center described by Thumas bears the same relation to the act of vomiting (and possibly to other functions) which the spinal cord bears to the many normal reflexes in which it is known to be concerned. We believe that afferent impulses more or less constantly, or, at least, frequently, pass from various peripheral organs, including the stomach and the heart, through the sympathetic to the center in the medulla of the normal animal, but that these normal impulses are too feeble to set up the powerful reflex concerned in vomiting which is accompanied by violent, and even convulsive, contractions of the diaphragm and abdominal muscles.

It is well known, of course, that sensory impulses pass almost constantly from various parts of the body to the cord and give rise to slight reflex movements or none. If one scratches the skin gently there is no perceptible reflex, but a violent scratch induces a prompt reflex movement. It is also well known, of course, that strychnin acts on the cord in such a way that the passage of impulses is facilitated so that gentle scratching of the skin then induces typical convulsions.

We believe that the direct action of apomorphin on the vomiting center in the medulla is wholly analogous to that of strychnin on the cord, and that when the reflex excitability of the center is increased by apomorphin emesis results from normal afferent impulses.

We have recently obtained evidence which we believe lends some support to the view that the vomiting center of Thumas is merely a mechanism for the coordination of the reflexes concerned with nausea and vomiting (and possibly with other functions) and while we do not wish to enter into a discussion of the details of these experiments at this time we wish to say that we have induced nausea in cats and dogs, with actual vomiting in one, by applying strychnin to the vomiting center. It is significant also that morphin causes apomorphin-like emesis in dogs and strychnin-like convulsions in frogs.

Vomiting is known to be induced by the action of toxic substances or by injuries affecting many organs, including the stomach, intestines, liver, uterus, kidneys, testicles, and brain, and the results of our work point to the heart also as the seat of reflex vomiting.

Since the various reflex paths are always ready for instant service, even in individuals who have never vomited, it seems reasonable to suppose that the tone of these paths is maintained in health by means

of impulses which traverse them constantly or frequently; for example those from the stomach when it contains food, those from the heart when there is any minor disturbance or change in rate due to sudden exertion, and it is well known that violent or prolonged exertion frequently induces nausea of greater or less severity.[8]

If our views are correct, nausea and vomiting are of fundamental importance for the protection of various organs and tissues against poisoning (using that term in its broadest sense) and different organs have developed this protective mechanism independently of the irritant action which these substances exert on the gastric mucous membrane. It is especially interesting in this connection to observe that rodents, which are incapable of vomiting, have developed several different, and apparently independent, methods of protecting themselves against the toxic action of digitalis bodies on the heart, and also against the injurious actions of various other vegetable poisons.

SUMMARY

1. Several of the digitalis bodies, including ouabain, amorphous strophanthin, digitoxin, digitalein and tincture of digitalis, were used in about eighty experiments designed to determine the seat of their emetic action in the cat and dog.

2. In one series of experiments the carotid and vertebral arteries were tied, after which the intramuscular or intravenous injection of ouabain or digitoxin caused nausea or vomiting. Two animals failed to vomit owing to severe depression.

3. Nausea and vomiting could not be elicited in cats by perfusing the brain and medulla with diluted defibrinated blood to which ouabain had been added.

4. Nausea and vomiting were induced in cats by the injection of ouabain into the femoral vein in experiments in which the poison was prevented from reaching the medulla by perfusing that organ with unpoisoned diluted defibrinated blood for a period of ten minutes, during which all but traces of the poison left the circulation.

5. Nausea or vomiting could not be induced in any of the experiments on fourteen cats and one dog in which ouabain, amorphous strophanthin, digitoxin, and digitalein were applied to the floor of the fourth ventricle—the vomiting center of Thumas—in widely varying amounts.

6. The application of small amounts of digitalis bodies to the floor of the fourth ventricle—the vomiting center—is without influence on the vomiting reflex and the subsequent intramuscular injection of ouabain or other digitalis body causes emesis in the same way as it

8. One of us is frequently troubled with nausea following certain types of moderate exertion that induce some cardiac irregularity and rapid pulse.

does in the normal animal. Large doses applied to this area depress the center, and vomiting cannot then be elicited by the intramuscular or intravenous injection of a digitalis body.

7. Apomorphin hydrochlorid causes emesis in dogs when it is applied to the vomiting center in amounts corresponding to 0.0001 mg. per kilogram of body weight.

8. Cutting the vagi at the level of the sixth cervical vetrebra (with tracheotomy) does not interfere with the emetic action of an intravenous injection of ouabain.

9. Section of the cord above the level at which the sympathetic cardiac fibers enter it, or removal of the stellate ganglia, usually prevents nausea and vomiting after the administration of digitalis bodies.

10. The severing of all nervous connections between the heart and the medulla always prevents nausea and vomiting after the injection of moderate doses of digitalis bodies.

11. Removal of the celiac plexus does not interfere with the emetic action of the digitalis bodies except in so far as the operation causes depression.

12. The administration of mercuric chlorid through a stomach tube in doses of 50 mg. per kilogram of weight causes emesis in cats in which the spinal cord has been cut at the level of the second thoracic vertebra and in those in which the stellate ganglia have been removed and the vagi have been cut.

CONCLUSIONS

Digitalis bodies cause reflex nausea and vomiting through their direct action on the heart.

The afferent impulses pass from the heart to the vomiting center in the medulla, by way of the sympathetic mainly, in part, by way of the vagus, probably.

Nausea and vomiting accompanying various circulatory disturbances, and more particularly those of cardiac origin, acquire a new interest for the clinician in the light of our results.

A theory relating to the physiology of nausea and vomiting is submitted.

THE ALKALI RESERVE IN PULMONARY TUBERCULOSIS *

DAVID S. HACHEN, B.S., M.D.
CINCINNATI

The question of acidosis in tuberculosis is still a debatable one. Pottenger [1] states that "there are probably many factors present in tuberculosis which have a tendency to increase acidosis, such as deficient intake of oxygen, deficient excretion of carbon dioxid, which occurs particularly in the disease, as a result of diminished pulmonary area, etc. Klebs [2] takes the opposite view, that "the gaseous metabolism in tuberculosis is but slightly, if at all, altered, the system accommodating itself to the lessened lung area, and, as is usual in the body, accomplishing the same amount of work with the decreased amount of tissue." A. Loewy, and Kraus and Chvostek [3] found a moderate increase in oxygen intake and carbon dioxid excretion in cases of pulmonary tuberculosis. It will be one of the objects of this work to show that in far advanced cases of pulmonary tuberculosis with considerable destruction of lung tissue by cavitation and caseous bronchopneumonia, there is only a slight decrease in the blood alkali reserve, at no time approaching a real acidosis.

The cases were carefully selected from 213 patients having every variety of lesion, the far-advanced type predominating. The method of Van Slyke [4] was used to determine the bicarbonate content of the blood plasma in terms of the percentage by volume of carbon dioxid. Using the precautions outlined by Van Slyke, 10 c.c. of blood was drawn from a median vein at the elbow, placed in a centrifuge tube containing 5 drops of a 20 per cent. solution of potassium oxalate, and covered with liquid petrolatum. The blood was centrifuged and the carbon dioxid combining power of the plasma determined within three hours in every instance. The temperature, pulse and respiration of each patient was taken from fifteen minutes to half an hour after the blood was drawn. The first specimen of urine passed by the patient following withdrawal of blood was examined for reaction, and at the same time tests for urochromogen and diazo substances were made. The reaction of the urine was determined by the use of a 0.2 per cent.

---

* From the Percy Shields Memorial Research Laboratory, Cincinnati Tuberculosis Sanatorium, and the Department of Bacteriology, University of Cincinnati.

1. Pottenger, F. M.: Clinical Tuberculosis, V. **1**:456, 1917.
2. Klebs, A. C.: Tuberculosis, 1909, p. 296.
3. Loewy, A., Kraus & Chvostek: quoted from Arnold Klebs.[2]
4. Van Slyke, D. D.: Method of determining carbon dioxid and carbonates in solution, J. Biol. Chem. **30**:347 (June) 1917.

solution of methyl red in alcohol. One drop of this reagent was added to 5 c.c. of clear urine in a test tube, the contents shaken and the color reading made by looking through the depth of the fluid. A distinct canary yellow color imparted to the urine was indicative of a urine alkaline to methyl red, i. e., having a hydrogen-ion concentration less than p_H 5; an orange color pointed to a urine neutral to methyl red; i. e., a hydrogen-ion concentration of p_H 5; while a red color showed a urine to be acid to methyl red or having a hydrogen-ion concentration greater than p_H 5.

An accurate check on the clinical conditions of the patients was kept, and the cases were classified in four groups as follows:

CONDITION 1.—"Up-patients," requiring only a minimum of rest hours. Clinically, these patients were in good condition, and usually did small chores in the ward kitchen or main dining room.

CONDITION 2.—Patients who were put to bed because they were coughing a little, running a slight afternoon fever denoting some active lung lesion. Clinically, these patients felt well and were kept in bed with difficulty. They were allowed toilet privileges only.

CONDITION 3.—These were bed-ridden patients, who ran a high afternoon temperature, i. e., over 100 F., coughed a good deal, produced considerable sputum daily, suffered with chills and sweats, and were slightly dyspnoeic at times. Clinically, these patients were manifestly ill.

CONDITION 4.—These patients suffered from an accentuation of symptoms outlined under Condition 3, and were considered in an immediately dangerous state. They would sometimes become slightly cyanotic with approaching death.

DATA AND RESULTS

The cases selected were males and females, white and colored, old and young, having every variety and severity of lesion. Sixty-seven determinations were made on sixty-one cases. In six cases, two determinations were made about a week apart in an endeavor to obtain records as close to death as possible.

A change for the worse in the clinical condition of the patient was always accompanied by a mild corresponding drop in the alkali reserve (Table 1).

In five of the six cases in which two determinations were made between five and sixteen days apart, a decrease of from two to eight points in the alkali reserve was noted (Table 2).

Comparison of the alkali reserve of the blood with the reaction of the urine in the bladder in a series of cases showed a tendency for the former to decrease, as the reaction of the urine passed from alkaline to acid (Table 3).

A comparison of the alkali reserve with the temperature of patients showed that an increase in temperature above 100 F. was usually accompanied by a drop in the alkali reserve (Table 4).

TABLE 1.—BLOOD ALKALI RESERVE OF SIXTY-ONE PATIENTS *

Clinical Condition	1	2	3	4
Number of Determinations	22	23	13	9
Alkali Reserve Range	48-70	50-73	52-62	50-62
Average Alkali Reserve	61.1	59.9	56.4	54.4

* Normal blood alkali reserve 53-78.

TABLE 2.—BLOOD ALKALI RESERVE IN SIX SPECIAL CASES

Case Number	*Date*	*Alkali Reserve*	*Clinical Condition*
E-186	3/31/21	56	III
	4/7/21	58	III
F-30	3/31/21	54	III
	4/7/21	52	IV
F-67	4/2/21	58	III
	4/18/21	50	IV
F-70	4/2/21	62	IV
	4/7/21	58	IV
E-178	4/2/21	60	III
	4/17/21	52	IV
E-308	4/7/21	62	III
	4/18/21	59	IV

TABLE 3.—COMPARISON OF ALKALI RESERVE WITH THE REACTION OF BLADDER URINE

Reaction of Urine	* *Alkaline*	*Neutral*	*Acid*
Number of Determinations	19	23	18
Range of Alkali Reserve	52-73	50-68	48-70
Average Alkali Reserve	61.1	58.0	57.7

* Alkaline to methyl red; hydrogen ion concentration less than *p*H5. Neutral to methyl red; hydrogen ion concentration, *p*H 5. Acid to methyl red; hydrogen ion concentration greater than *p*H 5.

TABLE 4.—COMPARISON OF ALKALI RESERVE WITH TEMPERATURE

Temperature	100 *F and under*	*Over* 100 *F*
Number of Determinations	37	27
Range of Alkali Reserve	48-73	50-69
Average Alkali Reserve	60.4	56.6

There was apparently no correlation between variations in the respiratory rate of patients and the blood alkali reserve. In fifteen cases with a respiratory rate over 25, the average alkali reserve was 58.0, as compared with an average alkali reserve of 57.3 in fifty-two

cases with a respiratory rate under 25. There was no correlation between variations in pulse rate and the blood alkali reserve. In seven cases where blood had been drawn one to sixteen days previous to death, the blood alkali reserve ranged between 50 and 58, the average being 52.7. Two cases of acute miliary tuberculosis, diagnosis verified at necropsy, had alkali reserves of 52 each. In one case the blood was examined forty-one days, in the other case seven days previous to death.

The existence of positive urochromogen or diazo substance in the urine was indicative of a tendency for the blood alkali reserve to diminish. Eleven cases giving positive reactions showed an average alkali reserve of 56.3. It will be noted in Table 1 that this figure is very close to the average found in patients designated Condition 3, this latter average being 56.4.

TABLE 5.—The Alkali Reserve in Cases with Extensive Lung Destruction Showing Number of Days Before Death Following the Last Alkali Reserve Determination

Case No.	Alkali reserve	No of days before death that alkali reserve was done
F-107	55	1
F-70	58	9
F-30	52	16
F-186	58	8
F-165	52	11
F-107	50	46
F-178	52	56
F-141	55	45
F-118	52	90
F-191	66	102
F-172	60	90
F-161	63	99

A careful study of the lung necropsy findings was made in twelve cases by Dr. J. B. Rogers. Every case revealed extensive lung destruction with fibrosis, cavitations and caseous bronchopneumonia, and yet the alkali reserve ranged between 50 and 63, the average being 56.2.

With the permission of Dr. J. B. Rogers a detailed account of the lung necropsy findings is given in the first three cases outlined in Table 5.

Case 1.—Alkali reserve 55, one day before death.

Right Lung.—Practically the entire upper lobe is occupied by active acute interlocular cavities surrounded by a caseous gelatinous pneumonia. The lower border of the middle lobe is occupied by caseous pneumonia, while the apex contains a cavity approximately one inch in diameter. The upper half of the lower lobe contains numerous cavities, while the lower half is infiltrated with caseous pneumonia.

Left Lung.—The outstanding feature is the presence of an empyema. A cavity is found rupturing into the pleural sac which contains approximately

500 c.c. pus. The entire lung is collapsed and compressed against the hilum. Both upper and lower lobes are excavated by multilocular cavities surrounded by fibrous tissue.

CASE 2.—Alkali reserve 58, nine days before death.

Right Lung.—The upper lobe is honeycombed by large multilocular cavities surrounded by a limited amount of fibrous connective tissue. The middle lobe contains numerous small cavities, one-half inch in diameter. The lower lobe is completely consolidated as a result of confluent caseation and broncho-pneumonia.

Left Lung.—The upper one half of the upper lobe contains large multilocular cavities, while the lower one half is infiltrated with caseous broncho-pneumonia. The upper one half of the lower lobe contains confluent caseous broncho-pneumonia.

CASE 3.—Alkali reserve 52, sixteen days previous to death.

Right Lung.—Practically the entire upper lobe is hollowed out by a cavity, which is surrounded by confluent caseous bronchopneumonia. The middle lobe is infiltrated with confluent caseous bronchopneumonia. The lower lobe contains scattered masses of caseous bronchopneumonia.

Left Lung.—At the apex there is a cavity about one inch in diameter, surrounded by caseous pneumonia. The remainder of the upper lobe is occupied by smaller cavities which are surrounded by caseous bronchopneumonia. The lower lobe contains patches of caseous bronchopneumonia.

The necropsy findings in the remainder of the cases are very similar to those described above, the alkali reserve of the blood being surprisingly high in some of the cases with extensive lung destruction. This state of affairs is in sharp contrast with that found in influenza and influenzal bronchopneumonia where the alkali reserve dropped as low as 24 in a severe case (Hachen and Isaacs [5]).

SUMMARY AND CONCLUSIONS

1. In tuberculosis there is a moderate depletion in the blood alkali reserve only after the lesion becomes far advanced and is accompanied by rather severe clinical symptoms, such as increased fever, chills and sweats, slight dyspnea and general malaise (Table 1).

2. The blood alkali reserve in an individual case continues to decrease slowly with approaching death until a minimum of 50 is reached (Table 2).

3. The blood alkali reserve was 3 points lower in cases where the urine as voided was neutral or acid to methyl red. An acid urine is, of course, not an indication that an "acidosis" exists (Table 3).

4. An increase in temperature above 100 F. was usually accompanied by a decrease in the alkali reserve (Table 4).

5. There was no correlation between the respiratory rate and the blood alkali reserve.

6. There was apparently no correlation between the pulse rate and the blood alkali reserve.

---

5. Hachen, D. S., and Isaacs, R.: The Alkali Reserve in Epidemic Influenza and Broncho Pneumonia, J. A. M. A. **75**:1624 (Dec. 1) 1920.

7. The alkali reserve was comparatively low (52) in two cases of acute miliary tuberculosis.

8. Urochromogen or diazo substance in urine was frequently found when the blood alkali reserve was relatively low.

9. In thirteen cases showing at necropsy extensive tuberculous involvement of all lobes, the average alkali reserve was 56.

10. Although there is a decrease in the alkali reserve as the case advances, at no time is there a marked "acidosis" in pulmonary tuberculosis.